Sugar Creek Cancer Inquiry Report
Level Three Investigation

MISSOURI DEPARTMENT OF HEALTH

Division of Chronic Disease Prevention and Health Promotion

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Introduction

In July 1998, residents living in Sugar Creek, Missouri (MO) contacted the United States (U.S.) Agency for Toxic Substances and Disease Registry (ATSDR) with concerns about a possible excess of brain cancer and other health problems in their neighborhood. They attributed the excess to possible environmental contamination from the former Amoco/Standard Oil Refinery located in the community. ATSDR referred their cancer concerns to the Missouri Department of Health's (MDOH's) Cancer Inquiry (CI) Program.

ATSDR reported to the CI Program that an area off-site of the former refinery where these residents live contains groundwater and soil that has been contaminated with benzene and other constituents of petroleum.[1] ATSDR concluded that a past, current and future completed exposure pathway to indoor air exists for residents living in closest proximity to the plant. It also concluded that the site represents an 'indeterminate public health hazard'. The CI Program contacted the two inquirers who reported eight cases of brain cancer in Sugar Creek. With this information, MDOH's Chronic Disease Medical Epidemiologist began research according to the approved MDOH four-stage protocol.[2] The CI Program concluded the Level 1 inquiry on October 23, 1998. It included basic research into citizens' concerns, case verification and a literature review to determine the types of cancer that have been linked to the suspected exposures of petroleum-derived constituents. After examining the available information, the CI Committee supported the Chronic Disease Medical Epidemiologist's recommendation to proceed to a Level 2 inquiry. This decision indicated there was enough evidence to conduct a preliminary scientific investigation into whether or not there is excess cancer in the area. The Level 2 inquiry involved rate estimation and a preliminary cluster investigation using incidence data from the Missouri Cancer Registry from 1985 through 1992 and mortality data from 1980 through 1996. The Level 2 results pointed to mixed evidence for an incident brain cancer cluster but showed no evidence of a cluster of incident cases of leukemia or lymphoma. In addition, it could not confirm any statistically significant clusters of brain, lymphoma or leukemia deaths.

Following the recommendation of the Chronic Disease Medical Epidemiologist, the CI Committee approved further investigation (i.e., a Level 3 inquiry) which focused on brain cancer incidence. Specifically, the Level 3 investigation aimed to determine if either a true cancer excess or a cancer cluster exists in the study area. Also, it aimed to make public health recommendations to the city of Sugar Creek about any potential cluster of brain cancer.

The analytical methods used in this investigation took into consideration the putative effect of potential past exposure to petroleum derivatives on brain cancer occurrence in Sugar Creek. During analyses of spatial clustering, it incorporated two possible pathways for exposure to petroleum derivatives: 1) inhalation of volatile gases emanating from groundwater and/or soil vapors seeping into household confined spaces; and 2) air pollution from petroleum by-products from refinery stacks. The investigation also assumed a latency period of at least 16 years, with brain cancer cases identified between 1985 and 1998 possibly being exposed to putative petroleum-derivative compounds before 1982 (i.e., when the Amoco refinery closed). This latency and natural history of brain cancer influenced the choice of temporal thresholds used in the evaluation of time clustering. Finally, it assumed that primary brain cancers of different histology (e.g., glioblastomas, astrocytomas and ependymomas) have a similar etiology. They were, therefore, analyzed as one type of cancer. This report presents results of this investigation.

Background

There are two categories of brain cancer: primary and metastatic.[3] Primary brain cancer is brain cancer that initiates in the brain. The most prevalent histologic types are astrocytomas and glioblastomas. Other types such as ependymomas, medulloblastomas and oligodendrogliomas are rare.[4] Metastatic brain cancer is cancer that has migrated to the brain after originating in another part of the body. It acts and is treated like the cancer of its place of origin.

There is an early peak in brain cancer incidence in infancy and childhood, a linear increase with age thereafter and another peak between the ages of 50 and 80.[5] Incidence rates for all types of brain cancer are higher in males than in females. Rates also appear to be much higher in whites than in African Americans. The incidence in urban areas is reported to be higher than rural areas.[5] However, many etiological studies have identified farming or living on a farm as a risk factor for brain cancer.[6,7]

Brain cancer is the thirteenth most common cancer in the U.S., with an annual age-adjusted incidence between 4.8 and 19.6 per 100,000 population. There is an average of 17,500 new cases of primary brain cancer per year in the U.S. A number of reports have demonstrated an increase in the incidence of brain cancer for all ages in the U.S. during the last thirty years.[4,8,9,10] Between 1973 and 1985, brain cancer incidence in the U.S. has increased 10.7%, with an average annual increase of 0.9%.[9] This increase was higher among the elderly, with average annual percentage increases ranging from 7.0% to 23.4% for those in age groups 75-85 and 85+, respectively. It has been reported that in Minnesota, age-adjusted incidence of primary tumors of the brain increased from 9.5 per 100,000 in 1950-1969 to 12.5 per 100,000 in 1970-1989.[11] It is likely that the 35% increase in childhood brain cancer incidence in the U.S. between 1973 and 1994 was partially due to better diagnosis, detection and reporting.[10]

Occupations suspected of having higher than average rates of brain cancer include petrochemical workers, rubber workers, electrical workers exposed to electromagnetic fields

(EMFs) and agricultural workers.[5] Paternal employment in a variety of occupations, including paper or pulp-mill workers, aircraft workers, electricians, electronic manufacturing workers, agricultural workers, metal workers, electrical assembly workers, machine workers, construction workers and tobacco industry workers, seems to increase the likelihood of having children who develop brain cancer, as does occupational exposure to chemical solvents, paint, aromatic amino and aromatic nitro compounds, aromatic hydrocarbons, non-ionizing radiation and creosote. Mothers who either inhaled chemicals during pregnancy or got them on their skin at their jobs also seem more likely to have children who develop brain cancer.

N-nitroso compounds are suspected of contributing to brain cancer.[5] Polycyclic aromatic hydrocarbons (PAHs), N-2-fluorenylacetamide, triazenes, symmetrical hydrazines, inhaled bis-chloromethyl ether, vinyl chloride, acrylonitrile and ethylene oxide can produce brain cancer in animals. Studies have linked pesticides, insecticides and herbicides to childhood brain tumors.

Excess brain tumors and high-dose ionizing radiation have well-established causal links.[5] Head trauma has also been suspected of increasing the risk of developing brain cancer. Barbiturate exposure, both prenatal and childhood, seems to be linked to childhood brain cancer. Prenatal exposure to alcohol is a suspected cause of brain tumors in children; alcohol consumption has also been linked to brain tumors in adults. There is a suspected, but not proven, link between tobacco use and brain cancer. Secondhand smoke has been linked with brain tumors through both prenatal and adult exposures.

Diseases that are associated with brain tumors include tuberculosis, peptic ulcer, immunodeficiency diseases, stroke, multiple sclerosis, epilepsy and other seizure disorders, breast cancer, renal cancer and meningitis.[5] Diabetes and allergic conditions seem to decrease the risk of one type of brain tumor. Some types of brain tumors are suspected to be associated with infections of *Toxoplasma gondii*, a parasitic protozoan. Maternal influenza and chickenpox during pregnancy are also suspected of causing brain tumors in children of these pregnancies.

Certain inherited conditions are linked to brain cancer and there appears to be an excess number of patients with blood type A among those with brain cancer.[5] Also, geographical clusters of hereditary syndromes (e.g., Li Fraumeni) have been linked to an excess of cancer, including cancer of the brain, in certain communities.[12]

A few inconclusive or mixed-results studies have examined environmental brain cancer clusters.[13,14,15] Discrete excesses of brain cancer deaths, sometimes statistically non-significant, have been extensively reported in occupational settings, particularly in the chemical and petrochemical industries.[16,17,18,19,20,21,] However, a thorough review and re-analysis of data from 100 national and international epidemiological studies on brain cancer mortality from 1974 through 1988 found standardized mortality ratio (SMR) of brain cancer among petrochemical industry workers similar to the general population[22]. A few of these studies have identified early employment as an associated factor, pointing to lack of environmental controls and greater exposure to chemicals in early years of these industries.[19,20] Findings from the reported studies and from preliminary investigation of this alleged cluster of brain cancer justified further investigation of a possible brain cancer excess in Sugar Creek.

Methods

Study population

We assessed excess and clustering of primary malignant cancer of the brain occurring between 1985 and 1998 in Sugar Creek, MO and the combined area of Jackson and Clay counties. We defined primary malignant cancer of the brain based on International Classification of Diseases for Oncology, Second Edition (ICD-0-2) codes: C71.0-C71.9 for topography; and 80001-97223 for morphology. (Note: Lymphomas of the brain and central nervous system were included in the previous Level 2 investigation of lymphomas.) The Missouri Cancer Registry (MCR), in cooperation with local hospitals and the Kansas Cancer Registry (KCR), conducted case ascertainment to assure that the CI Program had the most complete listing of cases possible. Local hospitals and KCR were asked to submit all cases of brain cancer diagnosed or treated at their facility between 1985 and 1998 in which the place of residence at diagnosis was Jackson or Clay county. The earliest period for which we could obtain cancer incidence information was 1985, the first full year in which reporting of cancer cases to MCR was mandated by the State.

This two-county area was investigated for three reasons. First, living cancer cases residing in the initial area of the investigation, i.e., Sugar Creek and surrounding ZIP codes, are likely to move within the two counties and be reported in the hospital cancer registries of these counties. Second, complete case ascertainment in the two counties was more feasible in a six-month period than in the state, allowing for a reduction in reporting bias introduced by using state rates in the analyses. Case ascertainment in this two-county area is more complete than in the state as a whole, where reporting completeness may be differential across hospital registries and/or years. Third, these two counties share more characteristics with the population of Sugar Creek and Independence than the population of the state that was used as reference in the Level 2 investigation.

For most of the analyses, the study populations were from five study areas in the combined counties. These five geo-areas allowed expansion of the investigation on spatial and time clustering of brain cancer to areas larger than Sugar Creek as indicated by the potential exposure pathways under investigation. We further defined the geo-areas based on the methodological limitations of case ascertainment, geo-coding and data manipulation necessary for statistical testing. Spatial and time clustering analyses did not include cases with incomplete addresses. Therefore, rate-based analyses used a slightly higher count of cases for some geo-areas than did spatial-time clustering analyses.

Initially, we used three different geo-areas of various sizes in the study. The first area comprised the incorporated areas of the cities of Sugar Creek and Independence (Appendices 1a and 1b). This area contributed 127 cases for both rate and cluster analyses. The second study area was based on eight ZIP codes serving the two cities (i.e., 64050, 64052, 64053, 64054, 64055, 64056, 64057 and 64058) (Appendices 2a and 2b). It contributed 133 and 132 cases to rate and cluster analysis, respectively. The third study area was based on Census block groups of the same two-city area. Spatially, this area was the largest of the three (Appendices 3a and 3b). Centered on Sugar Creek, this area extended at least four miles in all directions and contributed 150 cases to both rate and cluster analyses.

From the study area based on ZIP codes we generated three other geo-areas: 1) ZIP codes 64053 and 64054; 2) ZIP codes 64050, 64052, 64053 and 64054; and 3) ZIP codes 64050, 64053 and 64054. The geo-area of the combined two ZIP codes 64053 and 64054 i.e., the area in closest proximity to the former Amoco Refinery site, contributed 16 cases to both rate-based and cluster analyses. Based on preliminary reports by the Missouri Department of Natural Resources (DNR) and ATSDR, it is believed that any possible human exposure through volatile compounds in the water tables would be most concentrated in this area. The geo-area composed of ZIP codes 64050, 64052, 64053 and 64054 contributed 74 and 73 cases, respectively, for rate and cluster analyses. This area was investigated to help elucidate potential exposure due to plume dispersion in the air as suggested by studies on patterns of winds

reported by the Midwestern Climate Center of the National Weather Service (i.e., winds predominantly blow from the southwest to the northeast). The geo-area consisting of ZIP codes 64050, 64053 and 64054 contributed 46 cases to both rate analysis and one specific cluster analysis for detecting departure from background rate (i.e., Pearson test).

For analyses of clustering using adjacent areas and rate estimation, we defined 38 small areas consisting of collapsed ZIP codes to achieve a population of at least 10,000 persons for each small area. Rate estimates involving either a small denominator (i.e., less than 10,000 persons) or a small numerator (i.e., less than 10 observations) are deemed unstable for calculations.[23,24]

We ascertained 866 cases in Jackson and Clay counties reported to MCR between 1985 and 1998, from which we excluded 149 cases from final analysis. Excluded were: 77 cases of benign tumors of the brain; 33 duplicates; two cases without date of birth; two cases without date of diagnosis; four cases without complete information on tumor type; four cases that occurred before 1985; and 27 cases not residing in Jackson or Clay county at time of diagnosis. Of the 717 incident brain cancer cases in the two-county area, 698 had a street address and 679 could be address-matched using geographical software.

Analysis

Descriptive

We examined brain cancer cases by date of diagnosis (1985 to1998), residence at diagnosis (all ZIP codes in Jackson and Clay counties), sex (male or female), and race (grouped as white or "other"). We categorized age at time of diagnosis in five age groups: 0-13, 14-44, 45-64, 65-74, or 75 and up. We analyzed incidence data of primary brain cancer cases only.

We examined the demographic distribution of brain cancer cases in Sugar Creek and compared it to that in the two-county area, other studied geo-areas and Missouri. We also compared the distribution of brain cancer cases to that reported in the literature.

We examined data for evidence of spatial clustering by visually inspecting surface density maps depicting cancer incidence in the two-county area. We examined the occurrence of cases to determine if they were distributed in the random pattern expected or if they grouped together in some way. Using twenty-year meteorological reports of the Midwestern Climate Center of the National Weather Service on intensity and frequency of direction of winds, we determined prevailing winds in the Sugar Creek area and assessed occurrence of cases in the areas covered by the winds.

Software and Type of Maps Used

With one exception, the maps for this project were produced with ArcView 3.1, a microcomputer-based geographic information system (GIS) program.[25] Thematic maps were used to illustrate the relative magnitudes of phenomena by geographic location. Dot maps (e.g., Figure 2 and Appendices 1a-3b) use points to communicate spatial density of discrete geographic phenomena. These maps illustrate well the residence location of persons with brain cancer. Choropleth mapping (e.g., Figures 3-9) employs distinctive shadings to illustrate variation from place to place in accordance with values they represent. This technique best displays differences of variables with the various enumeration units employed in the study.

Given that population density is an important variable in examining the distribution of cases across space, a map was created that combined the strengths of dot and surface mapping (Figure 1). This was done in ArcInfo 7.1, a leading GIS program operating on the UNIX platform.[26] Population, at the various scales employed in this study, is best represented as a continuous surface. This method compensates for a major limitation of choropleth mapping, which assumes a uniform distribution of a phenomenon across each defined zone and abrupt changes at boundaries. Enumeration districts used by the U.S. Bureau of the Census are designed to facilitate the counting of people, not to illustrate the natural spatial extent or the continuous nature of the many variables reported in their zones. To create the population

density surface, the geographical center was first identified for each of the 15,299 Census blocks in the two-county study area. A standardized attribute value was attached to each block centroid based on the total number of people in the Census block divided by its area. Because considerable variation can occur between and among contiguous blocks, values from other center points within a 50-meter radius of each centroid were used to create a smoothed value. These derived values were then used to create a relief surface based on population density. Finally, locations of brain cancer cases were laid on top of the density model.

Rate Calculation

We computed crude and age-standardized incidence rates for Missouri, Jackson County, Clay County, the combined two-county area and five geo-areas in three time periods: 1985-1992, 1993-1998 and 1985-1998. Using 1990 Census-based population estimates at the ZIP code level,[27] case series ascertained for this study from 1985 through 1998 and the 1970 U.S. standard population, we calculated directly age-adjusted rates in the combined two-county area, Jackson county, Clay county and five geo-areas. We used 1990 Census-based annual estimates of the Missouri population, MCR data from 1985 through 1992 and the 1970 U.S. standard population to directly standardize Missouri incidence rates. After collapsing ZIP codes to obtain populations with at least 10,000 residents, we estimated age-adjusted incidence rates of brain cancer for 38 small areas during the entire study period (i.e., 1985-1998) using direct standardization. We used 1990 Census-based estimates of the population size to calculate rates for each of the 38 small areas. We used the two-county population as the standard for direct and indirect rate standardization in the 38 small areas to minimize reporting bias to MCR.

We used the two-county area age-specific incidence rates of brain cancer to generate expected number of brain cancer cases and calculate age standardized incidence ratios using indirect methods for each of the five geo-areas in the three time periods and each of the 38 small areas during the entire study period.[28]

All rate calculations used population estimates from the 1990 Census, based on inter-census annual estimates by MDOH. It was assumed that population in each of the five geo-areas and 38 small areas was constant over the study period. This assumption was valid for Sugar Creek (i.e., ZIP codes 64053 and 64054) from 1990 to 1997, based on data from inter-census population estimates from MDOH (data not shown). Because rates were calculated for a period (i.e., average rate), and not a given year in the period (i.e., annual rate), violation of this assumption was minimized. If true annual rates were increasing or decreasing in the period, the true average rate would be similar to that estimated at mid-point in the period.

Cluster Analysis

We also investigated clustering of cancer cases in time, in space (i.e., spatial clustering) and in time and space simultaneously, using several statistical methods.[2,29]

We used the Texas method and Poisson estimated probabilities to assess increases over time of brain cancer occurrence above background levels (i.e., expected number of cases for combined areas of Jackson and Clay counties during the 1985-1998 period).[2,29] The Texas method and Poisson estimated probabilities allowed for the calculation of indirectly standardized incidence ratios (SIR). We estimated SIR for the three time periods, (i.e., 1985-1992, 1993-1998 and 1985-1998).

We evaluated spatial clustering using Ohno and Grimson methods based on adjacencies of one or more of each of 38 small geographical areas with a high incidence rate.[2,28] The Grimson and Ohno tests require spatial adjacencies and rate calculation for each study area before calculations are run. We chose ZIP codes as the spatial unit of analysis (Appendix 4). Due to the small population (i.e., under 10,000) and number of cases (i.e., often less than five cases) of some areas, we combined certain ZIP codes in order to calculate stable rates (Appendix 5). Before aggregating ZIP codes, we considered several socioeconomic variables to prevent dissimilar areas from being combined. These included the percentage of white and African-

American population, percentage of population classified by the U.S. Bureau of the Census as "poor" or "very poor," percentage of population with no college education and median rent. The area aggregation based on socioeconomic indices aimed to produce small areas that were homogeneous regarding these factors, so that if a spatial clustering were found, it would be more likely that factors other than socioeconomic caused the difference. There are two ways of defining adjacency for a geographic area. The first considers ZIP codes as adjacent or "joined" only if they share a common border. The second broadens the definition of adjacency to also include nodes, or areas that only share a single point. Using the latter, more acceptable definition of adjacent area,[29] we counted adjacency in two ways: 1) combining ZIP codes 64053 and 64054; and 2) separating the two ZIP codes. This sensitivity analysis aimed to detect spatial clustering attributed either to the combined area or each of the separated zip codes.

We used Pearson test statistics to evaluate departure from random occurrence of brain cancer cases within geographical cells, after creating geographic small areas that contained similar population densities.[2,29] The Pearson test assumes cells of equal population. Given that population can vary considerably across space, we created cells based on population density estimates. This was accomplished by first determining the number of people per square mile for the Census block groups that comprise the ZIP codes of 64050, 64053 and 64054. Next, we laid a grid with 0.25 mile (0.4 km) resolution across the area. ArcView assigned the population density value of the block group enumeration area found at the center of each cell. At the end of this stage, we generated 317 cells that contained values ranging from 0 to 7,483. The mean population density was 2,120, with a standard deviation of 1,658. We combined adjacent cells to reduce variation in population density. Following this aggregation, there were 122 cells with values ranging from 4,254 to 7,532. This produced a mean population density of 5,263, with a standard deviation of 859. While the low value in the aggregated cells is not ideal, we were constrained by the Pearson requirement of a large ratio of cells to cases. Given that the study area had 41 cases, we aimed to have at least 120 cells. Any further combination of cells was thus prohibited. With the cells now defined, we counted the number of brain cancer cases found in each cell. Using the same cells, we repeated the process after eliminating ZIP code

65050 to create a cell count for Sugar Creek alone (i.e., Zip codes 64053 and 64054). The recalculation resulted in 46 cells and 16 cases with mean population density of 4,913 and a standard deviation of 909.

We made two additional cell counts for the Pearson test. We placed uniform grids over both Clay and Jackson counties. The first count used a cell resolution of one kilometer, while the second had a resolution of one mile. In order to reduce population variance, we counted cells for all resolutions after exclusion of unpopulated cells. However, either the requirement of having at least three cells per case or the assumption that population size for each cell was the same could not be met for the two additional resolutions of one kilometer and one mile.

We used the Knox and Barton methods to evaluate space and time interaction of brain cancer clusters during the study period.[2,29] Both the Knox and Barton statistical tests require longitude and latitude coordinates. To generate the needed coordinate pairs, we placed a uniform grid over the study area (i.e., geo-area). We located a 0,0 point on the bottom left corner of each study area so that all coordinates would be positive numbers. Each cell was given a unique X, Y coordinate pair. ArcView assigned the longitude and latitude to each case based on the X, Y coordinate pair of the cell in which each case was located. We used two a priori thresholds for spatial closeness of 1 mile (1.6 km) and 2 km (2.2 miles). We used a priori thresholds for closeness in time of one-year, two-year, four-year and seven-year periods. We also performed sensitivity analysis using other thresholds for closeness in space and time.

We evaluated clustering in time using the Chen and Scan methods. Both methods used date of diagnosis and monthly-based time windows to generate expectations of number of cases per time interval. We used two a priori defined time windows in the Scan test, 12 months and 84 months. We applied both statistical tests for time clustering using five related populations data as created for Barton and Knox X-Y coordinate-based analyses.

Because of the non-parametric nature of the tests used and the multiple testing approach with an inflated Type-I error rate, we considered results statistically significant if the probability of occurrence of an event as large or larger than observed was less than one in one hundred. We considered it borderline if this probability was between one in one hundred and five in one hundred. We considered mixed evidence of clustering when two methodologically-related and similar tests produced conflicting results.

Address Matching

Before any mapping or spatial analysis could occur, all cases had to be address matched. This involved finding the residence location and linking it to geographic areas recognized and coded by the U.S. Census.

The address-matching process involved two files. One file was the 1998 Topological Integrated Geographic Enumerated Regions (TIGER) file, a digital street map which describes the locational coordinates of the centerline of all streets, the range of street addresses that are found on each street segment and the different political and administrative areas to which each side of each street line segment belongs. The U.S. Bureau of the Census has developed TIGER line files to describe the street centerline map of the U.S. and Census Geography. The second file contained the street address descriptions of the brain cancer cases.

Of the 698 cases in Clay and Jackson counties with street addresses, we address matched 679 cases. This represented an overall 97.1% successful addressed-match rate, which is extremely high by GIS industry standards. Unmatched cases were the result of the case file not being compatible with the digital street map. This can happen because of inaccuracies or inconsistencies in the digital street map or because of inaccuracies or inconsistencies in the file of addresses to be matched.

Results

The 16 brain cancer incidence cases in Sugar Creek were mostly white male (not shown in tables) and between the ages of 40 and 75 (partially shown in Table 1). In Sugar Creek, the majority of cases occurred in the period 1985-1992 (data not shown in tables). The 717 cases in Jackson and Clay counties were predominantly male, older than 30 years of age and of white race (data not shown in tables). Demographic characteristics of incident cases in Sugar Creek and other study geo-areas were similar to those reported in the literature.[5] Study area populations were predominantly younger than 45 years of age, with a relatively even split of males and females (Table 2).

Age-adjusted incidence rates for Jackson and Clay counties, Jackson County, Clay County and the four geo-areas defined by ZIP code (i.e., ZIP codes 64050, 64052-64058; 64050, 64052-64054; 64050, 64053 and 64054; and 64053-64054) were higher than state rates in the 1985-1992 period (Table 3). For both the 1985-1992 and the 1993-1998 periods, three of the four geo-areas experienced age-adjusted incidence rates higher than the two-county area or each county alone (i.e., Jackson or Clay). The age-adjusted incidence rate for one geo-area, the one composed of ZIP codes 64053 and 64054 (i.e., the Sugar Creek area) was higher for the earlier period (i.e., 1985-1992) but not for the later period (i.e., 1993-1998).

In Missouri, the age-adjusted brain cancer incidence rate for the period 1985-1992 was 5.7 per 100,000 persons a year. It increased from 5.4 per 100,000 in 1985 to 6.6 per 100,000 in 1998 for a period percentage change of 22.2% (data not shown in tables). From 1985-1992 to 1993-1998, the age-adjusted incidence rate decreased 3.7% in Jackson County while it increased 10.8% in Clay County. The age-adjusted rate in the two-county area remained stable between time periods. Between 1985-1992 and 1993-1998, the age-adjusted incidence rate increased 7.9% for the largest of the ZIP code-defined geo-areas (i.e. 64050 and 64052-64058). During the same time, age-adjusted incidence rates decreased 51.2% for Sugar

Creek; 18.6% for the geo-area defined by ZIP codes 64050, 64052-64054; and 13.4% for the geo-area 64050, 64053 and 64054.

For the 1985-1992 period, the age-adjusted incidence rate was highest for Sugar Creek (i.e., 12.12 per 100,000 person years), decreasing concomitantly for other geo-areas defined by including zip codes further from Sugar Creek. This pattern is nearly reversed for the 1993-1998 period, with Sugar Creek experiencing the lowest incidence rate (i.e.,5.91 per 100,000).

During the study period 1985-1998, there was evidence of departure from expected incidence rate over time as determined by indirect methods of standardization in two geo-areas but not Sugar Creek (Table 4a). SIR in the geo-areas ranged from 1.18 to 1.56. Although SIR for Sugar Creek was 1.56, this was not statistically significant (i.e., P-value=0.058). SIR for all four geo-areas exceeded alert, but not action, level based on active surveillance methods applied to the retrospective case series. Looking only at the earlier period of 1985-1992, we identified a statistically significant excess occurrence of brain cancer cases in Sugar Creek and two other geo-areas in close proximity to and including Sugar Creek (Table 4b). SIR for Sugar Creek during this period was 2.05. The other two significant SIR were 1.43 and 1.46, respectively, for ZIP codes 64050, 64052-64054 and 64050, 64053-64054. None of the geo-areas studied experienced significant excesses in the 1993-1998 period (Table 4c).

A visual spatial analysis of the maps reveals that most brain cancer cases occurred in densely populated areas (Figure 1). Except for 14 cases, the remaining 703 incident brain cancer cases occurred in densely-populated urban areas across the two-county area (Figures 1 and 2). Following the Southwesterly direction of prevailing winds in the Sugar Creek area, we found only one case of brain cancer within a 10-mile (i.e., 16 km) span northeast of Sugar Creek. Brain cancer case density was higher in densely populated areas, particularly in seven small areas of the metropolitan Kansas City area southwest of Sugar Creek (Figure 3). Case density was moderate in the Sugar Creek geo-area. Sugar Creek and five other small areas scattered

across the two-county area were categorized in the top distribution of age-adjusted brain cancer incidence rates (Figure 4).

Age-specific incidence rates of brain cancer showed Sugar Creek as having: no cases for age groups 0-13 and 75+; and medium to high rates for age groups 14-44, 45-64 and 65+ (Figures 5-9). Many other small areas in the two-county area displayed similar rate distribution by age groups.

There was no evidence of departure from randomness in spatial distribution of incident cases for the Sugar Creek geo-area (i.e., 64503-64504) (Table 5). Using the Pearson statistic, the majority of geo-cells (i.e., 34 cells) had no cases, nine had one case, two had two cases and one had three cases. After expanding the study area with inclusion of ZIP code 64050, the Pearson statistic approaches borderline significance due to two additional cells with three cases located about 1.8 miles southeast of the refinery plant in ZIP code 64050.

There was no evidence of spatial clustering of brain cancer cases in Jackson and Clay counties as determined by the Ohno and Grimson methods using adjacent areas determined with inclusion of nodes (Tables 6a and 6b). Using the Ohno method, we found that number of observed and expected adjacent areas in the same rate categories and with high incidence rates were similar across study areas. In the adjacency area evaluation with the two collapsed Sugar Creek ZIP codes (64053 and 64054) and counting nodes, there were 40 observed and 34.53 expected concordant adjacencies (Table 6a). Using the Grimson test, a variation of the Ohno test, we found that among concordant observed adjacencies, 21 were areas with high rates of cancer; among concordant expected adjacencies, 17.24 were high-rate areas (Table 6b). Analysis with the two Sugar Creek ZIP codes as separate and independent areas did not change results of the Ohno and Grimson methods. We found 47 observed and 41.50 expected adjacencies (Table 6a). We identified 22 of the observed and 19.54 of the expected concordant adjacencies classified as high rate areas (Table 6b).

There was no evidence of simultaneous clustering of incident cases in space and time for any of five studied areas as demonstrated by using the Knox method and a priori thresholds for space and time closeness (Table 7a). Even after implementing sensitivity analysis with additional thresholds, we did not find evidence of simultaneous space and time clustering.

Using the Barton method, we found borderline statistical evidence of space and time interaction in the occurrence of a brain cancer cluster in Sugar Creek alone (i.e., ZIP Codes 64053 and 64054) (Table 7b). There was a stronger statistical evidence of space and time interaction in the occurrence of cluster for the other four geo-areas included in this analysis. The geo-areas comprised the combined Independence and Sugar Creek cities (i.e., Census block, incorporated area/political boundaries and eight ZIP codes (64050 and 64052-64058)) and an expanded area around Sugar Creek that included ZIP codes 64050 and 64052-64054.

Using the Scan method, we found no evidence of time clustering in Sugar Creek or any of the other four geo-areas of Jackson and Clay counties, even when we tried different time windows (Table 8a). The Chen method detected time clustering of borderline significance in Sugar Creek and two other geo-areas (i.e., one composed of eight ZIP codes and another defined by political boundaries) (Table 8b). There was no evidence of time clustering in the geo-area including Sugar Creek and adjacent ZIP codes (i.e., 64050, 64052-64054) and the area defined by Census block groups.

In summary, only two out of nine statistical tests conducted for clustering showed statistically significant evidence of clustering in Sugar Creek and two larger geo-areas in close proximity to and including Sugar Creek (i.e., geo-areas composed of ZIP codes 64053 and 64054; ZIP codes 64050 and 64052-64054; and ZIP codes 64050, 64053and 64054) (Table 9). The surveillance-based tests (i.e., Texas and Poisson) showed that there is statistical evidence of excess incidence compared to background rate in the period 1985-1992, suggesting a possible time clustering. However, incidence in these geo-areas declined to levels lower than in comparison to the two-county area in the period 1993-1998. In four large and densely

populated urban geo-areas that include Sugar Creek but that are centered within a radius of four miles south and eleven miles east of Sugar Creek, there is mixed evidence of simultaneous time-space clustering (i.e., Barton and Knox tests). However, for Sugar Creek alone, the evidence for simultaneous time and space clustering is weak. None of the geo-areas showed evidence of spatial clustering (i.e., Ohno and Grinsom tests). In three geo-areas, including Sugar Creek, there is mixed and weak (i.e. test results of borderline significance) evidence of time clustering as measured by the Chen test. Only one geo-area (i.e., ZIP codes 64050 and 64053-64054) showed weak evidence of departure from a background occurrence as demonstrated by the Pearson test.

Discussion

Brain cancer incidence rates in the study two-county area, Sugar Creek and two geo-areas were high but within the expected range observed for other counties in Missouri (data not shown in tables) and that reported for other states and the U.S.[8,9,10,11] Age-adjusted incidence rates for other counties in Missouri ranged from 1 per 100,000 to 23 per 100,000 person-years .

From 1985 to 1998, the brain cancer incidence rates in five studied geo-areas, including Sugar Creek, were higher than in the two-county area and Missouri. The incidence rate in Sugar Creek significantly exceeded the expected background rate of the two-county area in the 1985-1992 period only. Likewise, two other geo-areas (i.e., ZIP codes 64050, 64052-64054; and 64050, 64053-64054) experienced significant increases compared to background rates in the same time period. These excesses disappeared during the 1993-1998 period, with Sugar Creek experiencing significant incidence rate reduction between the two periods and showing the lowest rate for the latter period.

Because the majority of cases in Sugar Creek occurred in the early study period, it is possible that we only examined the end of a time cluster, with increased incidence prior to the study period being followed by the observed decrease. On the other hand, surveillance-based tests for evaluating time clusters (i.e., Texas and Poisson) are sensitive to small variations in case expectation.[2] The assumptions about geo-area population stability, change in population age-distribution over time and adequate allocation of cases to geo-areas with changing ZIP codes over time could all hamper the accuracy of expectation- and SIR-based analyses. Also, the observed increases in the incidence of brain cancer in Sugar Creek and two other geo-areas for the 1985-1992 period may represent two larger epidemiological phenomena. Brain cancer incidence increases have been reported for the U.S. and other regions during the same period.[3,6] The observed increases were possibly due to improvement in diagnostic techniques, greater accessibility to health care and/or secular trends linked to increases of risk factors that are currently unknown. In addition, it is possible that the excess of brain cancer occurrence in

Sugar Creek and two other geo-areas are also a reflection of true excesses common to urban areas. Cancer occurrence is known to be higher in urban settings.[3,5] These geo-areas are predominantly urban and the absolute majority of the brain cancer cases occurred in the most densely populated areas.

Albeit non-significant statistically for the majority of tests utilized, the analyses demonstrated mixed evidence of spatial and time clustering of brain cancer in a region wider than the study area of Sugar Creek. The evidence is mixed because methods that should be in agreement are not: Barton, but not Knox; Chen, but not Scan test. This wide area is composed of two buffers, one centered within a five-mile radius east of Sugar Creek and the other, within a six-mile radius south of Sugar Creek. The buffers roughly correspond to the geo-areas consisting of ZIP codes 1) 64050 and 64052-64054 and 2) 64050,64053 and 64054, respectively. This conclusion is supported by observation through geographical mapping, rate calculations and findings of the adjacency-based spatial clustering. We found a disproportional number of observed concordant pairs with high incidence rates located in these two geo-areas. Also, inclusion of ZIP code 64050 to the Sugar Creek area (i.e., ZIP code 64053 and 64054) to create another geo-area, led the Pearson statistic from a non-significant to a nearly significant finding due to the addition of two small geographical cell with three cases of brain cancer each. Four of the nine statistical tests demonstrated either elevation in cancer occurrence or clustering in these geo-areas. Because the areas are very large, even if a true cluster had been identified, it is unlikely that the cluster would be associated with a unique risk factor.

One should exercise caution in interpreting these findings. It is expected that results of analytical methods used to evaluate clustering of events will be consistent in the presence of true clustering.[29] In this analysis, the analytical methods are in disagreement in determining the presence of clustering. Nevertheless, it is possible that technical limitations in defining a geographical area, time windows or calculating rates could create spurious results that may overlook a true cluster. Also, we accepted a somewhat stringent but less conservative probability level when interpreting statistically significant results than recommended.[28]

Therefore, we likely increased our chances of making a Type-I error beyond what is usually stipulated and may have labeled some findings significant when they were not. Nevertheless, we conclude that, on average, we missed true clusters with low probability and rejected false clusters with higher probability.

Common limitations of cancer cluster investigations are discussed in the *Missouri Department of Health Cancer Inquiry Protocol* manual and other sources.[2] These investigations are usually plagued by methodological factors with potential to impact calculations of expected values and standardized morbidity ratio.

The accuracy of information on demographics and identifiers makes it difficult to prepare data for spatial clustering investigation. For example, inaccurate name and address information prevented the inclusion of 42 incident cases in the cluster analysis not based on rate estimation and expectation. However, none of these cases were originally from Sugar Creek. Moreover, changes in ZIP codes over time force the researcher to make arbitrary assumptions about the number of cases for specific small areas. In the analyses involving small areas, only three cases had to be re-allocated due to a ZIP code change from the year of diagnosis to the index year of geographical analysis, 1993.

Incomplete or inaccurate information on risk factors and occupation precluded meaningful comparisons of sub-populations and generation of hypotheses on the etiology of cancers being studied. In addition, because of incomplete reporting to the Missouri Cancer Registry for the period between 1993 and 1995 and changing trends in brain cancer incidence over the study period, we did not generate expectations or calculate age-adjusted rates based on state rates. Instead, we used the two-county area population and age-specific rates as an indirect standard to generate rates and expectations for the five geo-areas and 38 small areas of collapsed ZIP codes being compared.

The lack of population estimates by demographics for small areas in a given year or period of years precluded calculation of disease rates for some of the geo-areas (e.g., Census block groups). It also imposed assumptions about population stability on the calculation of rates and expectations of cancer occurrence. For example, the expected incidence of cancer used in this analysis assumed that the size and age distribution of the study populations remained constant from 1985 to 1998. Although the Sugar Creek population remained somewhat constant in size between 1990 and 1997 (data not shown in tables or appendices), it is unlikely that the age distribution throughout the period remained the same as in the 1990 Census. In addition, it is unlikely that population of other highly urbanized geo-areas remained constant over the 14-year period. Nevertheless, calculation of average rates (i.e., period rates) diminish as the danger of this assumption by estimating the rate at mid point in the period.

The possibility of incomplete reporting of cancer incidence to the Missouri Cancer Registry may impact cluster research. Reporting that is different for distinct areas will result in biased comparisons of cancer occurrence by geographical area. Underreporting in one area will make that area's observed occurrence of cancer smaller compared to other areas. Using data available from this investigation's case ascertainment and that in MCR, we estimated MCR's underreporting of brain cancer in Jackson and Clay counties to range from 5% to 35% for any given year in the study period (data not shown in tables). Consequently, the observed incidence rate in study areas tends to be larger than the state rate. We attempted to minimize this bias in our comparison of rates by using data from a two-county area in which case ascertainment was more complete than the rest of the state. With the help of all hospitals in Jackson and Clay counties, the Kansas Cancer Registry and data available in MCR, we ascertained more cases per year in the 1985-1992 period than had previously been reported to MCR. Also, use of geographical software mapping and Census data improved definition of study areas and underlying populations.

In addition to problems with case ascertainment, defining actual size of a population and population stability over time, rates for small areas tend to be unstable because of small

population and number of cases. We expanded the study area to increase the population size and number of cases. Also, when creating small geo-areas for rate calculation, we collapsed ZIP codes to generate areas with at least 10,000 persons each, which allowed us to calculate more stable rates. Moreover, average rate estimation for a period of years included adequate number of cases for most geo-areas studied. Therefore, we expect that error in rate estimation attributed to small numbers were minimized in our analysis.

It is possible that different types of brain cancer have different causes. Brain cancers with different sub-types and histology may well represent different diseases from an etiological standpoint. Therefore, the lack of evidence of a brain cancer cluster does not preclude existence of histology specific brain cancer in the area of study.

The goal of this research was to examine excess in the occurrence and clustering of cancer cases. This type of study cannot establish a causal association between a disease and risk factors. Nevertheless, a study area may be used as a proxy for possible environmental causes of cancer. This rationale, however, may be flawed by the aggregation of the associations being examined. This ecological fallacy precludes drawing causal inferences from this study.

Summarizing, only two out of nine statistical tests showed statistical evidence of either space or time clustering in Sugar Creek. If a possible environmental contamination was causing cancer within a 1.5-mile (2.4 km) radius of the Amoco plant site in Sugar Creek in the 1985-1998 period, we expected that the majority of tests would show evidence of clustering in this area.

In addition, we expected that similar tests would corroborate each other's findings (e.g., Poisson-based, Scan and Chen; Knox and Barton; Ohno and Grimson). Finally, technical limitations common to small area analysis may affect conclusions on rate estimates and time-cluster analysis based on expected number of cases. Therefore, it is possible that the observed pattern of brain cancer occurrence in Sugar Creek during the study period could have occurred by chance alone. On the other hand, it is also possible that a cluster might have occurred in an

earlier period for which data is unavailable. The incidence rate and rate-based time cluster analyses using expected number support this latter hypothesis. All other spatial and time cluster analyses do not.

Conclusions

- Demographic characteristics of brain cancer cases in Sugar Creek were similar to those of brain cancer cases of comparison populations (i.e., four geo-areas of Independence, the combined area of Jackson and Clay counties, the state of Missouri and that reported in literature).
- Between 1985 and 1998, incident brain cancer cases studied occurred predominantly in urban, densely-populated areas of Jackson and Clay counties, including Sugar Creek, as demonstrated by the population surface density map and SIR.
- The brain cancer age-adjusted incidence rates in two large urbanized geo-areas that included Sugar Creek (i.e., ZIP codes 64050 and 64052-64054; and ZIP codes 64050, 64053 and 64054), were higher than the two-county area or Missouri for all periods studied. Incidence rates in the two areas decreased substantially from 1985-1992 to 1993-1998. In Sugar Creek alone, the brain cancer age-adjusted incidence rate was significantly higher than in the two-county area or Missouri for the 1985-1992 period. During the 1993-1998 period, the brain cancer age-adjusted incidence rate significantly decreased in Sugar Creek to a level lower than the two-county area.
- During the 1985-1992 period, the observed number of brain cancer cases in Sugar Creek and two other geo-areas was significantly higher than expected based on the two-county area as demonstrated by calculation of SIR. During the 1993-1998 period, the observed number of brain cancer cases was significantly lower than expected.
- There is little evidence of spatial and mixed evidence of time clustering of brain cancer cases in Sugar Creek for the period 1985-1998. Only two out of nine statistical tests showed statistical evidence of either space or time clustering in Sugar Creek.
- There is mixed evidence of time and space clustering of brain cancer cases in two urbanized geo-areas larger than Sugar Creek but including the city of Sugar Creek (i.e., geo-areas composed of 1) ZIP codes 64050 and 64052-64054; and 2) ZIP codes 64050, 64053 and 64054).

- In Sugar Creek, statistical analysis shows that we cannot rule out chance as an explanation for the observed occurrence of brain cancer between 1985 and 1998.
- Due to the many and important limitations of this type of research, interpretation of these findings must be cautiously weighed.
- This type of research is limited to hypothesis generation and cannot examine causal associations.

Recommendations

- At present, further brain cancer cluster investigation in Sugar Creek and surrounding ZIP codes is unwarranted, other than continued active surveillance of incidence and mortality of a larger geo-area that includes the cities of Sugar Creek and Independence (i.e., ZIP codes 64050 and 64052-64058).
- The feasibility of implementing an etiological study on the causes of brain cancer in Missouri needs to be evaluated.
- Continued monitoring of petroleum-derived environmental contaminants identified in Sugar Creek[1] is warranted because of the potential public health hazard of contaminants.
- Either replication of this study or rigorous review of its methods and results are welcome to assure that the findings were not due to technical limitations in data preparation and manipulation.

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Table 1: Characteristics of Brain Cancer Incidence Cases in Study Population 1985-1998

	Case Series 1[1]	Case Series 2[2]	Case Series 3[3]	Case Series 4[4]	Case Series 5[5]	Case Series 6[6]	Case Series 7[7]
Age	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)
<14	71 (9.9%)	9 (6.0%)	8 (6.0%)	8 (6.3%)	5 (6.7%)	3 (6.4%)	0 (0.0%)
14-44	201 (28.0%)	44 (29.3%)	45 (33.6%)	40 (31.5%)	22 (29.3%)	17 (36.2%)	6 (37.5%)
45-64	216 (30.1%)	47 (31.3%)	39 (29.1%)	37 (29.2%)	22 (29.3%)	13 (27.7%)	5 (31.3%)
65-74	126 (17.6%)	31 (20.7%)	29 (21.6%)	28 (22.0%)	15 (20.0%)	10 (21.3%)	4 (25.0%)
≥ 75	103 (14.4%)	19 (12.7%)	13 (9.7%)	14 (11.0%)	11 (14.7%)	4 (8.5%)	1 (6.3%)
Total	717	150	134	127	75	47	16
Gender							
Male	385 (53.7%)	77 (51.3%)	71 (53.0%)	65 (51.2%)	42 (55.4%)	31 (65.2%)	13 (80.0%)
Female	332 (46.3%)	73 (48.7%)	63 (47.0%)	62 (48.8%)	33 (44.6%)	16 (34.8%)	3 (20.0%)
Total	717	150	134	127	75	47	16

[1] Case Series 1 includes all of Jackson and Clay Counties based on ZIP codes before 1993.
[2] Case Series 2 is broke out by census block groups
[3] Case Series 3 includes ZIP codes 64050, 64052-64058
[4] Case Series 4 is broke out by political boundaries
[5] Cases Series 5 includes ZIP codes 64050, 64052-64054
[6] Case Series 6 includes ZIP codes 64050, 64053 and 64054
[7] Case Series 7 includes ZIP codes 64053 and 64054. The number of cases in Series 7 may not match those in the analysis due to changes in ZIP codes over time.

Table 2: Characteristics of Underlying Population in Study Area 1985-1998

	Population 1[1]	Population 2[2]	Population 3[3]	Population 4[4]
Age	N	N	N	N
<14	160,214 (20.4%)	22,829 (19.3%)	10,563 (18.4%)	1,975 (18.5%)
14-44	378,030 (48.1%)	53,725 (45.4%)	25,500 (44.5%)	5,002 (46.8%)
45-64	149,903 (19.1%)	24,955 (21.2%)	11,370 (19.8%)	2,128 (19.9%)
65-74	56,396 (7.2%)	10,057 (8.5%)	5,672 (9.9%)	950 (8.9%)
≥ 75	42,100 (5.2%)	6,650 (5.6%)	4,260 (7.4%)	625 (5.9%)
Total	786,643	118,216	57,365	10,680
Gender				
Male	374,983 (47.6%)	56,342 (47.7%)	27,133 (47.3%)	5,297 (49.6%)
Female	411,660 (52.4%)	61,874 (52.3%)	30,232 (52.7%)	5,383 (50.4%)
Total	786,643	118,215	57,365	10,680

[1] Population 1 is all of Jackson and Clay Counties
[2] Population 2 Independence/Sugar Creek (ZIP codes 64050, 64052-64058)
[3] Population 3 is a break down of Independence/Sugar Creek (ZIP codes 64050, 64052-64054)
[4] Population 4 is Sugar Creek only (ZIP codes 64053 and 64054).

Table 3: Incidence Rate[1,2] for Missouri, Jackson and Clay Counties, and Geo-Areas for Three Time Periods: 1985-1992, 1993-1998, 1985-1998

Area	1985-1992		1993-1998		1985-1998	
	Crude	Age-Adjusted	Crude	Age-Adjusted	Crude	Age-Adjusted
Missouri	5.7	5.1	--	--	--	--
Jackson and Clay Counties	6.48	6.25	6.55	6.20	6.51	6.23
Jackson County	6.59	6.28	6.45	6.05	6.53	6.18
Clay County	6.03	6.18	6.95	6.85	6.43	6.47
ZIP codes 64050, 64052-64058	7.93	7.10	8.32	7.66	8.10	7.34
ZIP codes 64050, 64052-64054	10.24	8.97	8.14	7.30	9.34	8.26
ZIP codes 64050, 64053-64054	10.12	9.58	9.16	8.25	9.71	9.01
ZIP codes 64053-64054	14.04	12.12	6.24	5.91	10.70	9.46

[1] Rates per 100,000 person years were directly standardized using the 1970 US standard million population in five age categories (<14, 14-44, 45-64, 65-74, 75+).

[2] Rates calculated using case ascertainment series in Jackson and Clay counties, except for Missouri, calculated using MCR data.

Table 4a: Evaluation of Departure from Background Brain Cancer Incidence Rate (Poisson & Texas) for the Period of 1985-1998

Geo Area	# Cases in Time Interval	# Cases Expected in Time Interval	Alert Level	Action Level	SIR[1]	Conclusion	P(X ≥ x)
Independence Sugar Creek ZIP codes 64050, 64052-64058	134	113.38	1.126	1.290	1.18	Exceeds alert level but not action level	0.0523 (z = 1.94)
ZIP codes 64050, 64052-64054	75	57.72	1.176	1.407	1.30	Exceeds alert level but not action level	0.0164 (z = 2.27)
ZIP codes 64050, 64053, 64054	47	33.66	1.231	1.533	1.40	Exceeds alert level but not action level	0.0171 (z = 2.30)
ZIP codes 64053 & 64054[2]	16	10.26	1.418	1.965	1.56	Exceeds alert level but not action level	0.058 (z = 1.79)

[1] SIR=Standardized Incidence Ratio

[2] Number of cases observed using ZIP code definition before 1993. If we use only 15 cases based on new ZIP code definition, SIR=1.46 with corresponding P-value=0.0977.

Table 4b: Evaluation of Departure from Background Brain Cancer Incidence Rate (Poisson & Texas) for the Period of 1985-1992

Geo Area	# Cases in Time Interval	# Cases Expected in Time Interval	Alert Level	Action Level	SIR[1]	Conclusion	P(X ≥ x)
Independence Sugar Creek ZIP codes 64050, 64052-64058	75	64.7886	1.166	1.384	1.16	Below alert level	0.1154 (z = 1.27)
ZIP codes 64050, 64052-64054	47	32.9815	1.233	1.538	1.43	Exceeds alert level but not action level	0.0124 (z = 2.44)
ZIP codes 64050, 64053, 64054	28	19.2333	1.306	1.705	1.46	Exceeds alert level but not action level	0.0355 (z = 2.00)
ZIP codes 64053 & 64054	12	5.8587	1.554	2.277	2.05	Exceeds alert level but not action level	0.0171(z = 2.54)

[1] SIR=Standardized incidence ratio

Table 4c: Evaluation of Departure from Background Brain Cancer Incidence Rate (Poisson & Texas) for the Period of 1993-1998

Geo Area	# Cases in Time Interval	# Cases Expected in Time Interval	Alert Level	Action Level	SIR[1]	Conclusion.	P(X ≥ x)
Independence Sugar Creek ZIP codes 64050, 64052-64058	59	48.5914	1.192	1.443	1.21	Exceeds alert level but not action level	0.0807 (z = 1.49)
ZIP codes 64050, 64052-64054	28	24.7361	1.269	1.621	1.13	Below alert level	0.2813 (z = 0.66)
ZIP codes 64050, 64053, 64054	19	14.4250	1.369	1.814	1.32	Below alert level	0.1423 (z = 1.20)
ZIP codes 64053 & 64054	4	4.3940	1.639	2.474	0.91	Below alert level	0.6395 (z = 0.19)

[1] SIR=Standardized incidence ratio

Table 5: Brain Cancer Incidence - Departure from Randomness in Spatial Distribution (Pearson)

Geo-Area/ Resolution	# Cases/ Cell	# Cells	Expected Cells	X^2	DF	P-Value
64053 and 64054	0	34	32.36	0.082	1	>0.900
0.25 Miles[1]	1	9	11.51	0.591	1	>0.250
	2	2	1.92	0.003	1	>0.900
	3	1	0.21	1.511	1	<0.100
Total		46		χ^2_3=2.19	3	0.750>P>0.500
64050, 64053 and 64054	0	91	87.06	0.18	1	>0.500
0.25 Miles[2]	1	24	29.50	1.10	1	>0.250
	2	4	4.88	0.17	1	>0.500
	3	3	0.57	5.13	1	<0.025
Total		122		χ^2_3=6.564	3	0.050>P>0.025

[1]ZIP codes 64053 and 64054.
[2]ZIP codes 64050, 64053-64054.

Table 6a: Evaluation of Spatial Clustering (Ohno) - Jackson and Clay Counties

Data	Highest Rate	Lowest Rate	# of Adjacencies	Rate Category	Observed Adjacencies	Expected Adjacencies	Summary x^2 (OHNO)	P-Value
Counting Nodes[1, 2]	10.62	1.96	102	1.96-4.85 4.85-7.73 7.73-10.62	13 21 6	9.576 19.733 5.223	0.814 0.080 0.110	>0.300 >0.750 >0.750
Total					40	34.53	1.000	0.900
Counting Nodes[1, 3]	11.68	1.96	103	1.96-5.20 5.20-8.44 8.44-11.68	13 33 1	9.576 30.469 1.451	0.814 0.205 0.557	>0.100 >0.500 >0.05
Total					47	41.496	1.176	<0.50

[1]Adjacencies are determined by counting nodes (see methods)
[2]ZIP codes 64053 & 64054 are collapsed
[3]ZIP codes 64053 & 64054 are separated

Table 6b: Evaluation of Spatial Clustering (Grimson) - Jackson and Clay Counties

Data	Max Rate	Min Rate	Mean Rate	Smallest Rate Considered Large	Observed Adjacencies High Risk	Expected Adjacencies High Risk	Std. Dev. High Risk Adjacencies	Z Test	P-Value
Counting Nodes[1, 2]	10.62	1.96	6.00	6.50	21	17.24	3.02	1.24	0.214
Counting Nodes[1, 3]	11.68	1.96	6.15	6.50	22	19.54	3.14	0.783	0.108

[1]Adjacencies are determined by counting nodes (see methods)
[2]ZIP codes 64053 & 64054 are collapsed
[3]ZIP codes 64053 & 64054 are separated

Table 7a: Evaluation of Simultaneous Space and Time Clusters (Knox) – Brain Cancer Incidence

ZIP Codes/Grid Size	Critical Distance		# Pairs with Evidence of Clusters	Expected Pairs	Z	P(A≥OB/EP)
	Space	Time				
64053 & 64054/1 km	1	12	12 out of 120	11.800		0.5153
	1	84	47 out of 120	43.758		
64053 & 64054/1 km	2	12	19 out of 120	18.400		0.4751
	2	84	74 out of 120	68.233	0.698	0.2451
64053 & 64054/1 mile	1	12	15 out of 120	13.200		0.3454
	1	84	52 out of 120	48.950	0.436	0.3336
64053 & 64054/1 mile	2	12	22 out of 120	20.00		0.3563
	2	84	77 out of 120	74.167	0.329	0.3745
64050, 64052-64054/ 1 km	1	12	48 out of 2628	39.130	0.139	0.4483
	1	84	219 out of 2628	206.857	0.844	0.2005
64050, 64052-64054/ 1km	2	12	78 out of 2628	75.284	0.313	0.3783
	2	84	421 out of 2628	397.784	1.154	0.1251

Table 7a: Evaluation of Simultaneous Space and Time Clusters (Knox) – Brain Cancer Incidence

64050, 64052-64054/ 1 mile	1	12	67 out of 2628	72.046	-0.594	0.7224
	1	84	397 out of 2628	378.791	0.936	0.1736
64050, 64052-64054/ 1 mile	2	12	150 out of 2628	162.289	-0.965	0.8314
	2	84	857 out of 2628	853.260	0.128	0.4522
64050, 64052-64058/1km	1	12	59 out of 8646	62.281	-0.416	0.6591
	1	84	339 out of 8646	321.482	0.977	0.1660
64050, 64052-64058/1 km	2	12	125 out of 8646	130.598	-0.490	0.6879
	2	84	698 out of 8646	674.124	0.920	0.1789
64050, 64052-64058/1 mile	1	12	108 out of 8646	119.703	-1.070	0.8577
	1	84	642 out of 8646	617.884	0.970	0.1660
64050, 64052-64058/1 mile	2	12	266 out of 8646	286.079	-1.187	0.8810

Table 7a: Evaluation of Simultaneous Space and Time Clusters (Knox) – Brain Cancer Incidence

	2	84	1501 out of 8646	1476.689	0.633	0.2644
Census Block/1 km	1	12	63 out of 11175	66.668	-0.449	0.6736
	1	84	362 out of 11175	347.478	0.779	0.2207
Census Block/1 km	2	12	137 out of 11175	143.321	-0.528	0.7019
	2	84	763 out of 11175	747.000	0.585	0.2810
Census Block/1 mile	1	12	123 out of 11175	135.685	-1.089	0.8621
	1	84	728 out of 11175	707.201	0.782	0.2177
Census Block/1 mile	2	12	301 out of 11175	322.620	-1.204	0.8925
	2	84	1696 out of 11175	1681.000	0.353	0.3632
Political boundaries/1 km	1	12	59 out of 8001	60.473	-0.189	0.5754
		84	331 out of 8001	309.881	1.200	0.1151
Political boundaries/1 km	2	12	125 out of 8001	128.703	-0.333	0.6293

Table 7a: Evaluation of Simultaneous Space and Time Clusters (Knox) – Brain Cancer Incidence

		84	684 out of 8001	659.918	0.937	0.1736
Political boundaries/1 mile	1	12	19 out of 8001	18.778		0.5102
		84	97 out of 8001	96.222	0.079	0.4721
Political boundaries/1 mile	2	12	35 out of 8001	40.217	-0.823	0.7939
		84	216 out of 8001	206.082	0.691	0.2451

Table 7b: Evaluation of Space and Time Clusters Interaction - Brain Cancer Incidence (Barton)

Geo Area/Grid Size	Temporal Cells	Q	V(Q)	Std Dev (Q)	F	DF_n	DF_d	P-Value
ZIP Codes 64053 and 64054/1 km	8	1.2458	0.0410	0.20237	1.73	48	42	0.025<P< 0.05
ZIP Codes 64053 and 64054/1 mile	8	1.3271	0.0378	0.19455	2.12	52	45	<0.01
ZIP Codes 64050, 64052-64054/1 km	13	1.1009	0.0044	0.06646	2.22	451	90	<0.001
ZIP Codes 64050,64052-64054/1 mile	13	1.0923	0.0039	0.06283	2.03	505	101	<0.001
Independence/Sugar Creek ZIP codes 64050, 64052-64058/1 km	14	1.0624	0.0015	0.0382	2.45	1,367	151	<0.001
Independence/Sugar Creek ZIP codes 64050, 64052-64058/1 mile	14	1.0667	0.0013	0.0366	2.70	1,491	164	<0.001
Political boundaries of Independence/Sugar Creek/1 km	14	1.0469	0.0016	0.03963	1.755	1,272	146	<0.001
Political boundaries of Independence/Sugar Creek/1 mile	14	1.0470	0.0017	0.04085	1.771	1,190	138	<0.001
Census Block group division/1 km	14	1.0551	0.0012	0.03413	2.49	1,715	164	<0.001
Census Block group division/1 mile	14	1.526	0.0011	0.03311	2.34	1,823	174	<0.001

Table 8a: Evaluation of Clustering in Time (Scan)

Geo Area	Total # Cases[1]	Window (Months)	% 168 units of Time	# of Scanned Units	Max # of Cases/Window	Expected # Cases/Window	P(A ≥ a)
Census Block Group Jackson and Clay Counties	150	12	7.14	157	17	10.71	1.0000
	150	84	50.00	85	85	75.00	0.4479
Independence/ Sugar Creek ZIP codes 64050, 64052, 64053, 64054, 64055, 64056, 64057, & 64058	132	12	7.14	157	17	7.43	0.7628
	132	84	50.00	85	75	66.00	0.4859
Political Boundaries for Independence and Sugar Creek	127	12	7.14	157	16	9.07	1.0000
	127	84	50.00	85	71	62.39	0.6239
Independence and Sugar Creek ZIP codes: 64050, 64052, 64053 and 64054	73	12	7.14	157	9	5.21	1.0000
	73	84	50.00	85	42	36.50	0.6513
Sugar Creek ZIP codes: 64053 and 64054	16	12	7.14	157	5	1.14	0.1988
	16	84	50.00	85	11	8.00	0.5434

[1] Only address-matched cases used in analysis.

Table 8b: Evaluation of Clustering in Time (Chen)

Population	Geo Area	Study Period	Critical Interval	Observed # of Cases[2]	Expected # of Cases	All Pairs Close in Time	P-Value
Population: 118,216 Background Rate:[1] 6.5105	ZIP codes 64050, 64052-64058	167 months	5.91 months	132	107	129 out of 131 were close in time	0.0594
Population: 116,283 Background Rate:[1] 6.5105	Political Boundaries	167 months	5.95 months	127	105	124 out of 126 were close in time	0.0554
Population: 151,721 Background Rate:[1] 6.5105	Census Block groups	167 months	4.76 months	150	137	only 148 out of 149 successive cases were close in time	0.3426
Population: 56,365 Background Rate:[1] 6.5105	ZIP codes 64050, 64052-64054	155 months	10.46 months	73	47	only 71 out of 72 were close in time	0.1559
Population: 10,680 Background Rate:[1] 6.5105	ZIP codes 64053 & 64054	130 months	29.47 months	16	8	All cases occur in less than critical interval	0.0456

[1] Background rate is crude rate of Jackson and Clay counties combined: 6.5105 per 100,000.
[2] Only address-matched cases used in analysis.

Table 9 - Summary Results of Time and Space Clustering of Brain Cancer Evaluation in Combined Jackson and Clay Counties, Independence, and Sugar Creek

Geo-Area	Time and Space Clustering		Spatial Clustering		Time Clustering		Surveillance-Departure from Background Rate		Departure from Background Occurrence
	Knox	Barton	Ohno	Grimson	Scan	Chen	Texas	Poisson	Pearson
64053& 64054	No	Border line	No	No	No	Borderline	Yes	Yes	No
64050, 64053-64054	-	-	No	No	-	-	Yes	Yes	Borderline
64050, 64052-64054	No	Yes	No	No	No	No	Yes	Yes	-
64050, 64052-64058	No	Yes	No	No	No	Borderline	Borderline	Borderline	-
Block Group	No	Yes	No	No	No	No	-	-	-
Political Boundaries	No	Yes	No	No	No	Borderline	-	-	-
Jackson and Clay Counties	-	-	No	No	-	-	-	-	-

Figure 1

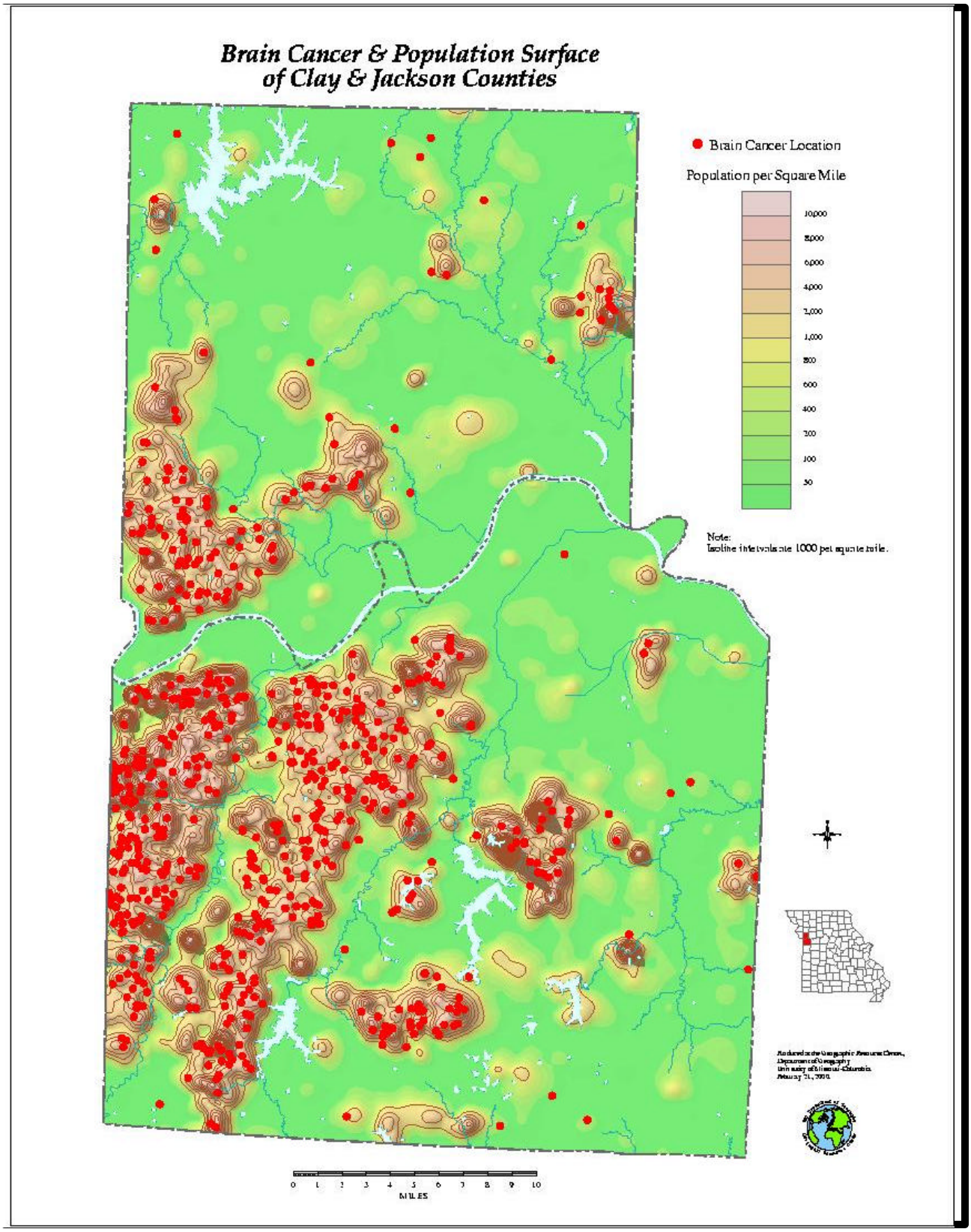

Brain Cancer & Population Surface
of Clay & Jackson Counties
Brain Cancer Location
Population per Square Mile
10,000
8,000
6,000
4,000
2,000
1,000
800
600
400
200
100
50
Note:
Isoline intervals are 1000 per square mile.
0 1 2 3 4 5 6 7 8 9 10
MILES

Figure 2

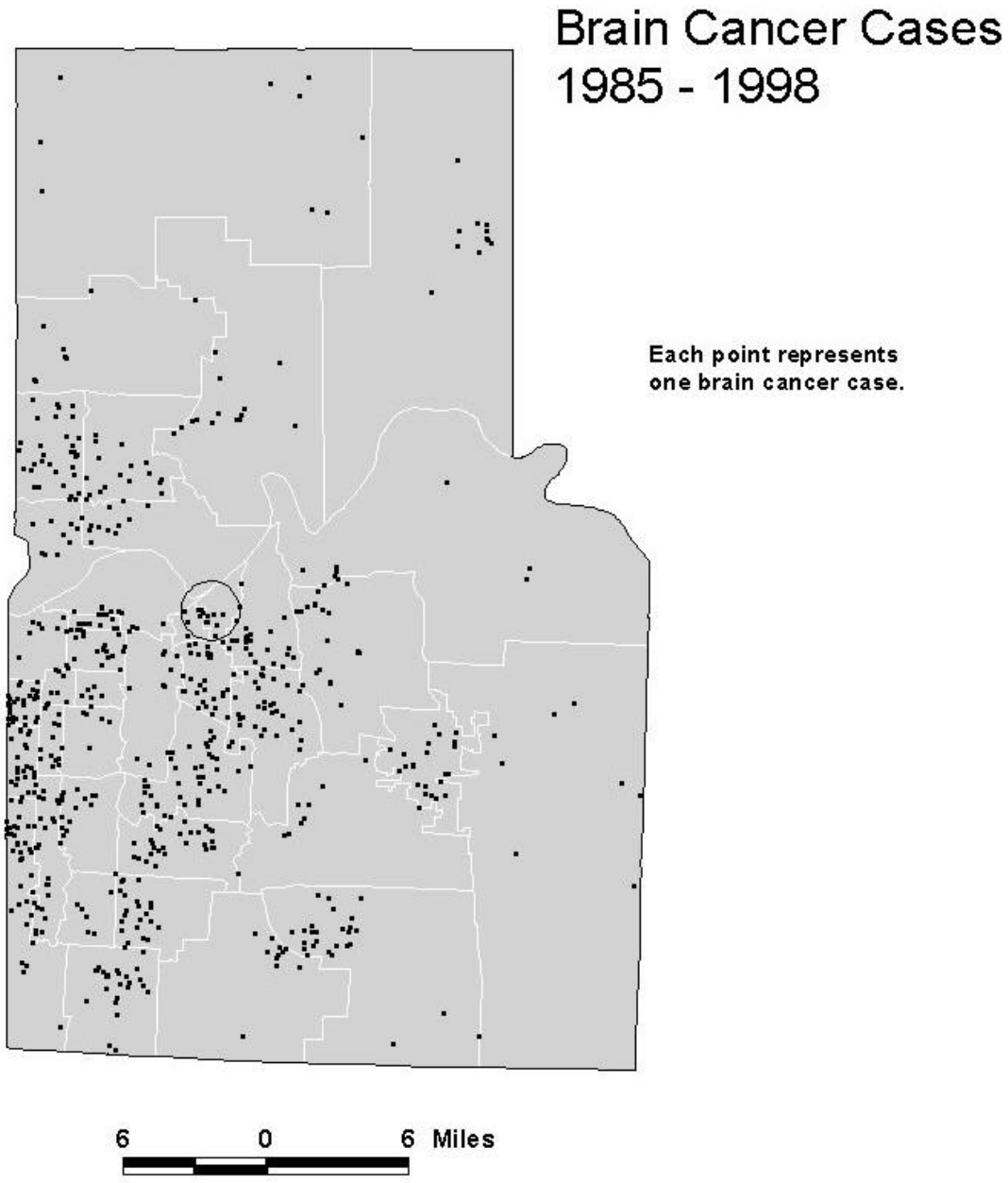

Brain Cancer Cases
1985 - 1998
Each point represents
one brain cancer case.
6
0
6 Miles

Figure 3

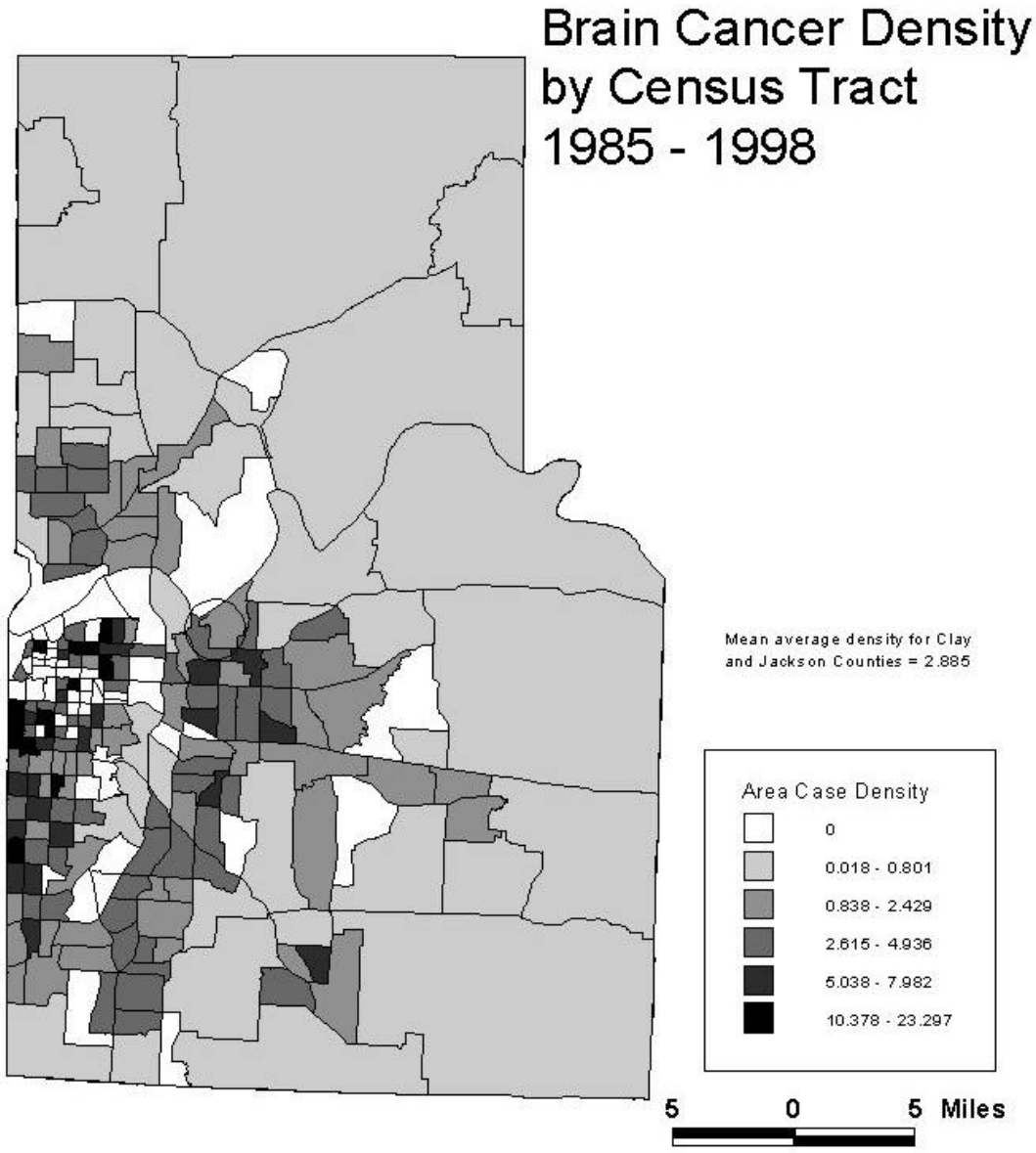

Brain Cancer Density
by Census Tract
1985 - 1998
Mean average density for Clay
and Jackson Counties = 2.885
Area Case Density
0
0.018 - 0.801
0.838 - 2.429
2.615 - 4.936
5.038 - 7.982
10.378 - 23.297
5 0 5 Miles

Figure 4

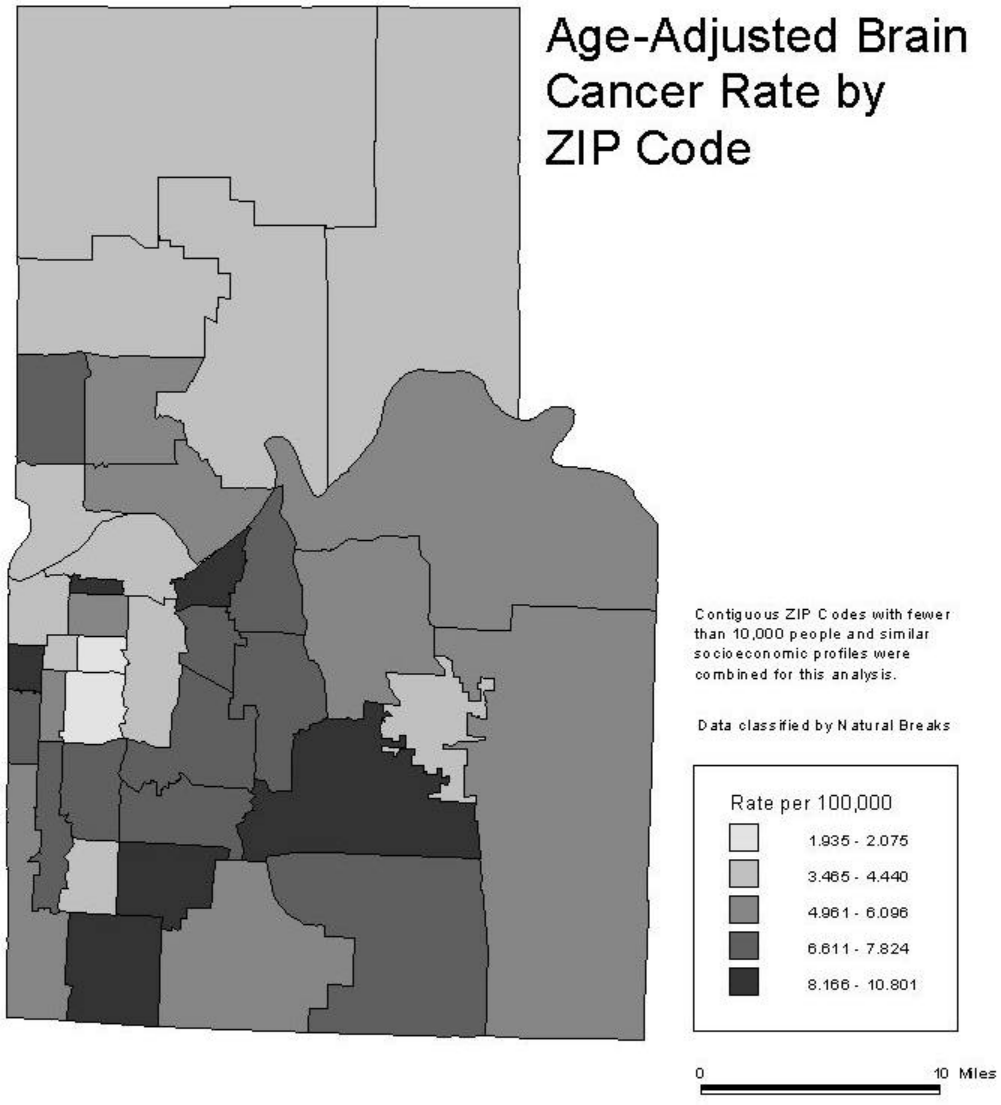

Age-Adjusted Brain Cancer Rate by ZIP Code
Contiguous ZIP Codes with fewer than 10,000 people and similar socioeconomic profiles were combined for this analysis.
Data classified by Natural Breaks
Rate per 100,000
1.935 - 2.075
3.465 - 4.440
4.961 - 6.096
6.611 - 7.824
8.166 - 10.801
0
10 Miles

Figure 5

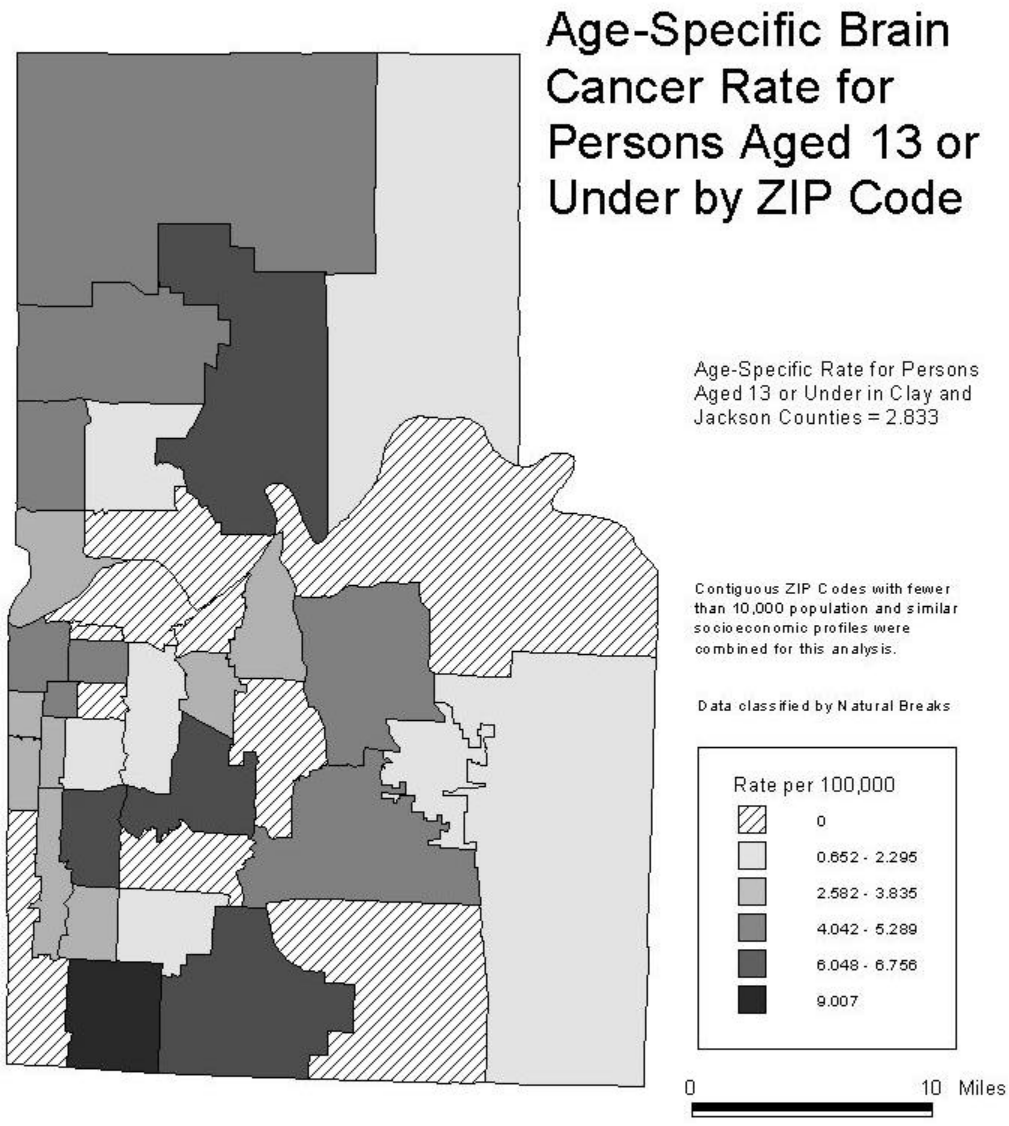

Age-Specific Brain Cancer Rate for Persons Aged 13 or Under by ZIP Code
Age-Specific Rate for Persons Aged 13 or Under in Clay and Jackson Counties = 2.833
Contiguous ZIP Codes with fewer than 10,000 population and similar socioeconomic profiles were combined for this analysis.
Data classified by Natural Breaks
Rate per 100,000
0
0.652 - 2.295
2.582 - 3.835
4.042 - 5.289
6.048 - 6.756
9.007
0
10 Miles

Figure 6

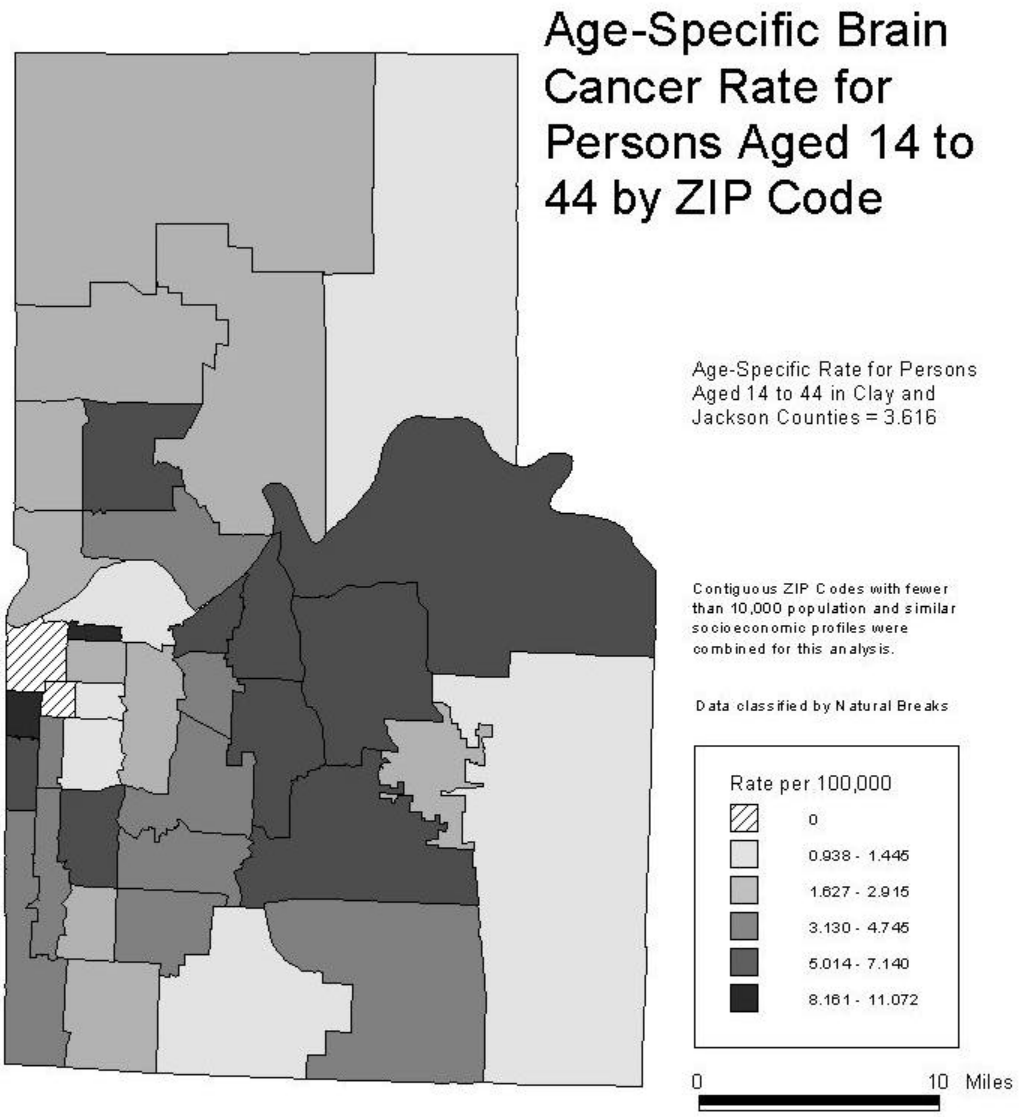

Age-Specific Brain Cancer Rate for Persons Aged 14 to 44 by ZIP Code
Age-Specific Rate for Persons Aged 14 to 44 in Clay and Jackson Counties = 3.616
Contiguous ZIP Codes with fewer than 10,000 population and similar socioeconomic profiles were combined for this analysis.
Data classified by Natural Breaks
Rate per 100,000
0
0.938 - 1.445
1.627 - 2.915
3.130 - 4.745
5.014 - 7.140
8.161 - 11.072
0
10 Miles

Figure 7

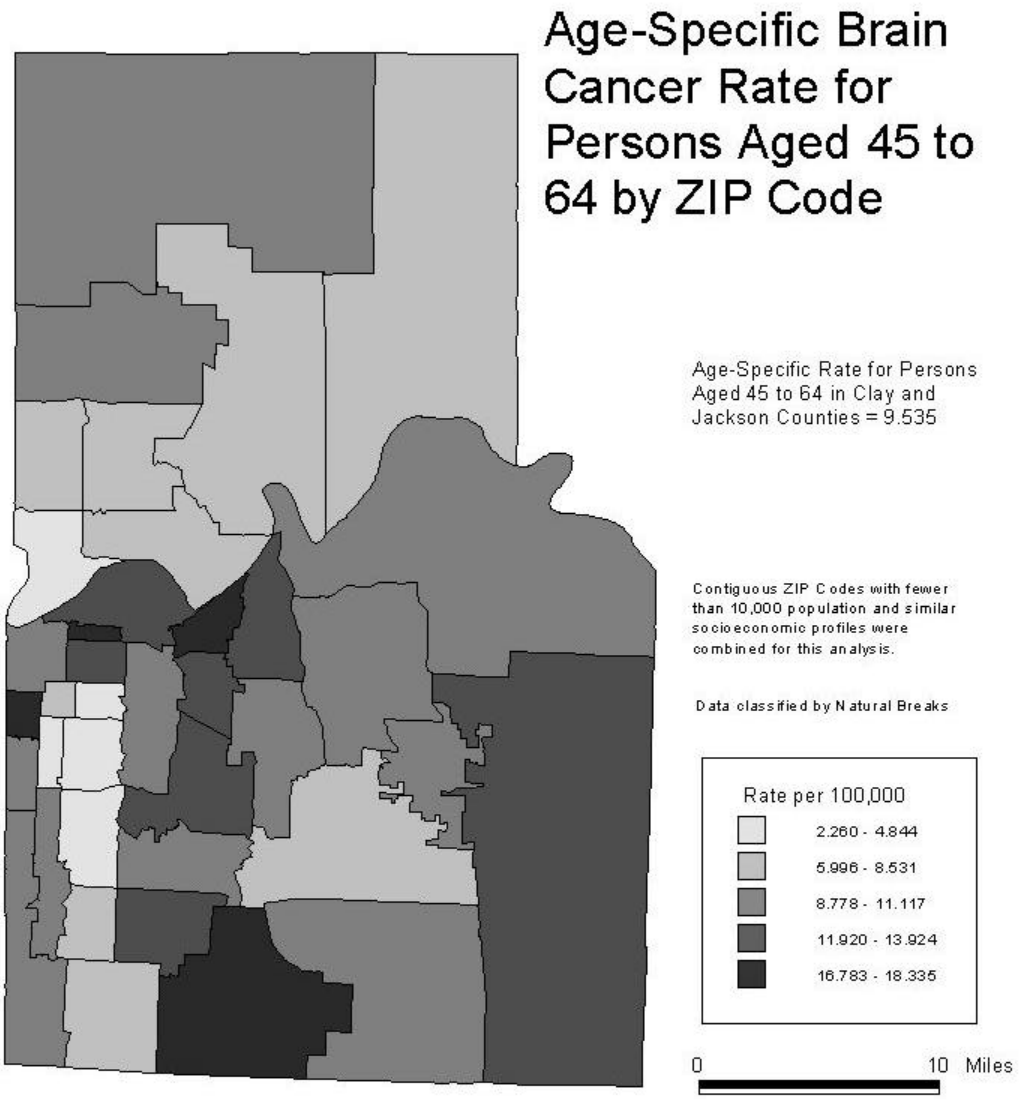

Age-Specific Brain Cancer Rate for Persons Aged 45 to 64 by ZIP Code
Age-Specific Rate for Persons Aged 45 to 64 in Clay and Jackson Counties = 9.535
Contiguous ZIP Codes with fewer than 10,000 population and similar socioeconomic profiles were combined for this analysis.
Data classified by Natural Breaks
Rate per 100,000
2.260 - 4.844
5.996 - 8.531
8.778 - 11.117
11.920 - 13.924
16.783 - 18.335
0
10 Miles

Figure 8

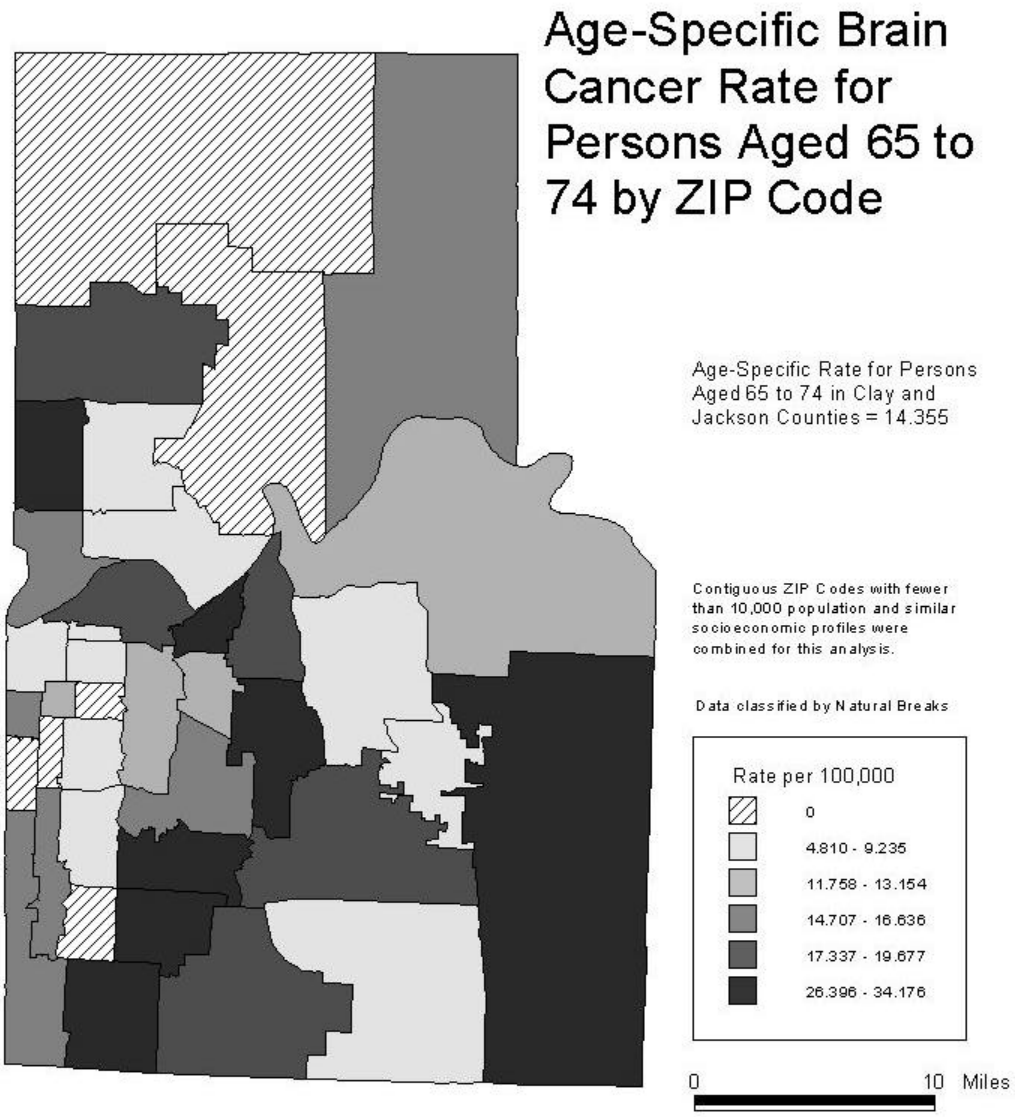
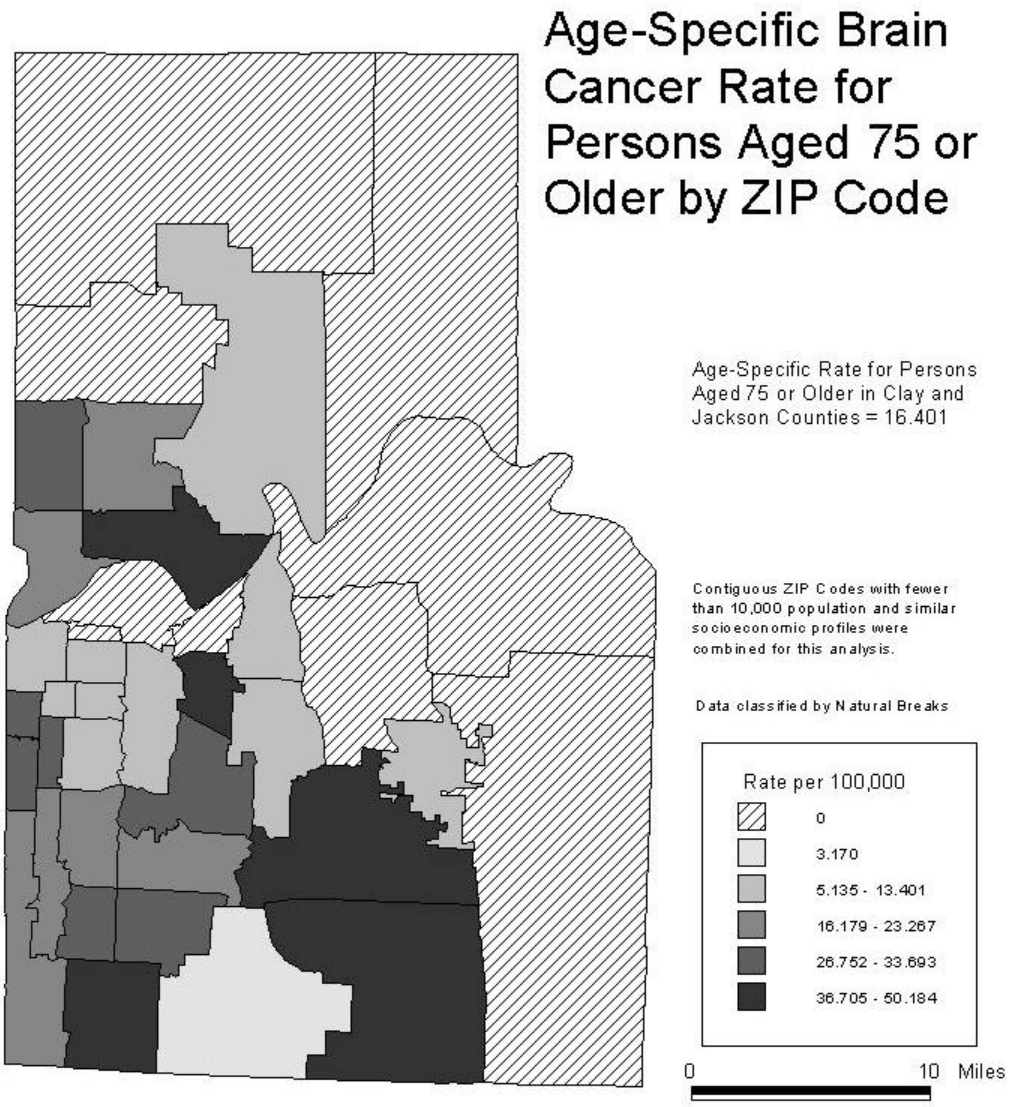
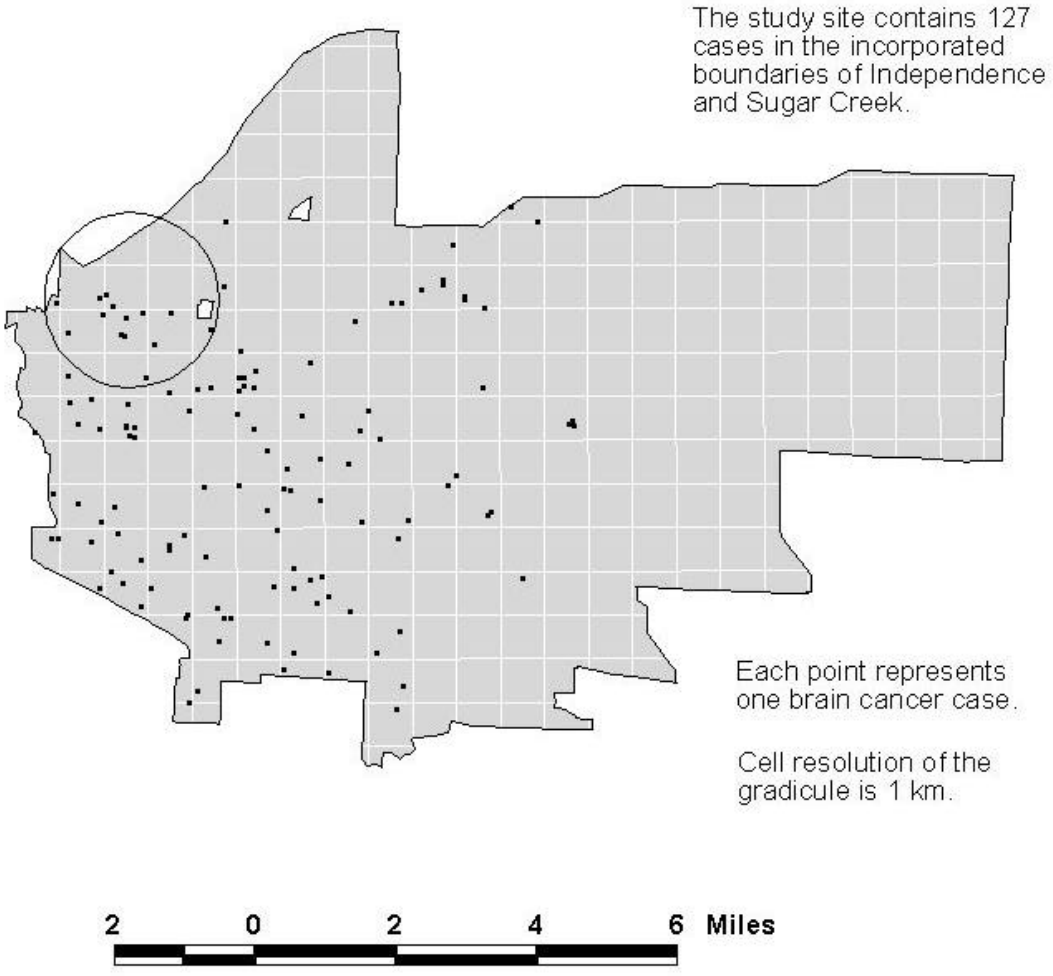

Age-Specific Brain Cancer Rate for Persons Aged 65 to 74 by ZIP Code
Age-Specific Rate for Persons Aged 65 to 74 in Clay and Jackson Counties = 14.355
Contiguous ZIP Codes with fewer than 10,000 population and similar socioeconomic profiles were combined for this analysis.
Data classified by Natural Breaks
Rate per 100,000
0
4.810 - 9.235
11.758 - 13.154
14.707 - 16.636
17.337 - 19.677
26.396 - 34.176
0
10 Miles

Figure 9


Age-Specific Brain Cancer Rate for Persons Aged 75 or Older by ZIP Code
Age-Specific Rate for Persons Aged 75 or Older in Clay and Jackson Counties = 16.401
Contiguous ZIP Codes with fewer than 10,000 population and similar socioeconomic profiles were combined for this analysis.
Data classified by Natural Breaks
Rate per 100,000
0
3.170
5.135 - 13.401
16.179 - 23.267
26.752 - 33.693
36.705 - 50.184
0
10 Miles

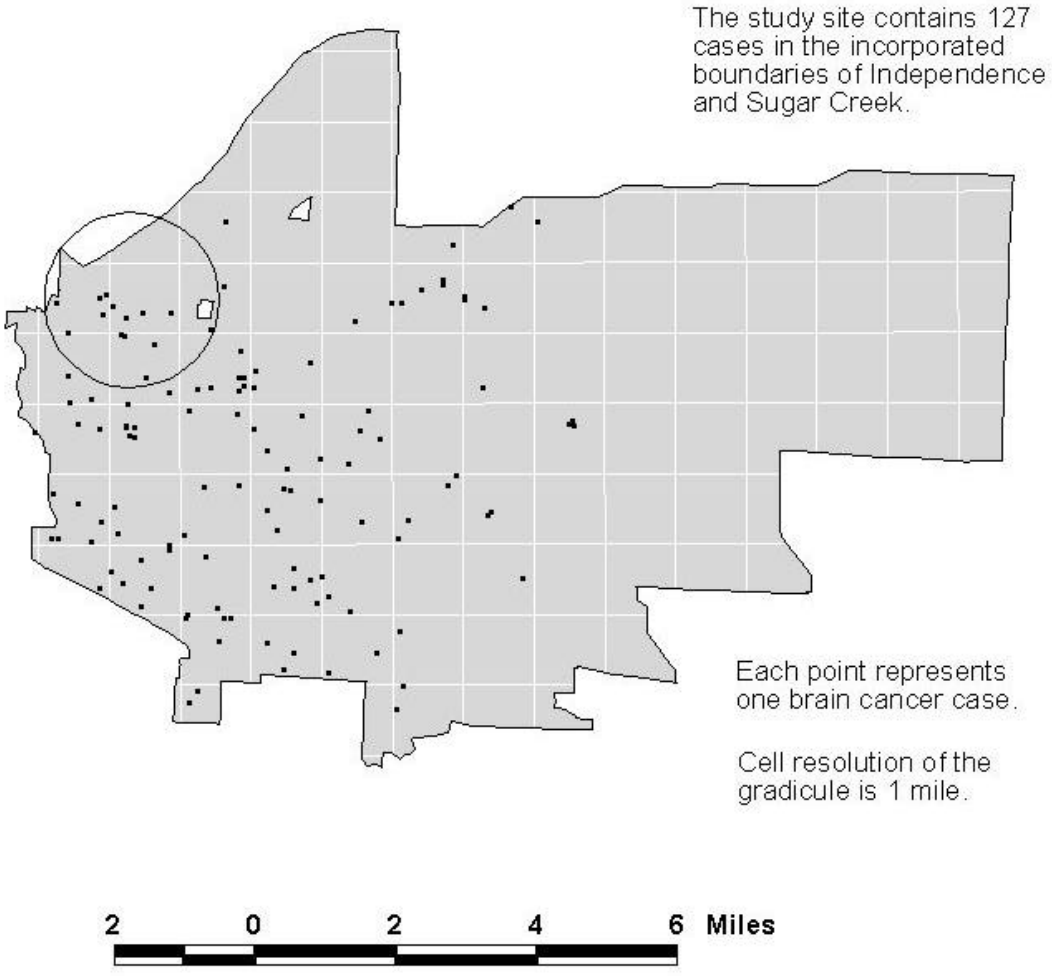
Appendix 1a

Study Site Based on Political Boundaries

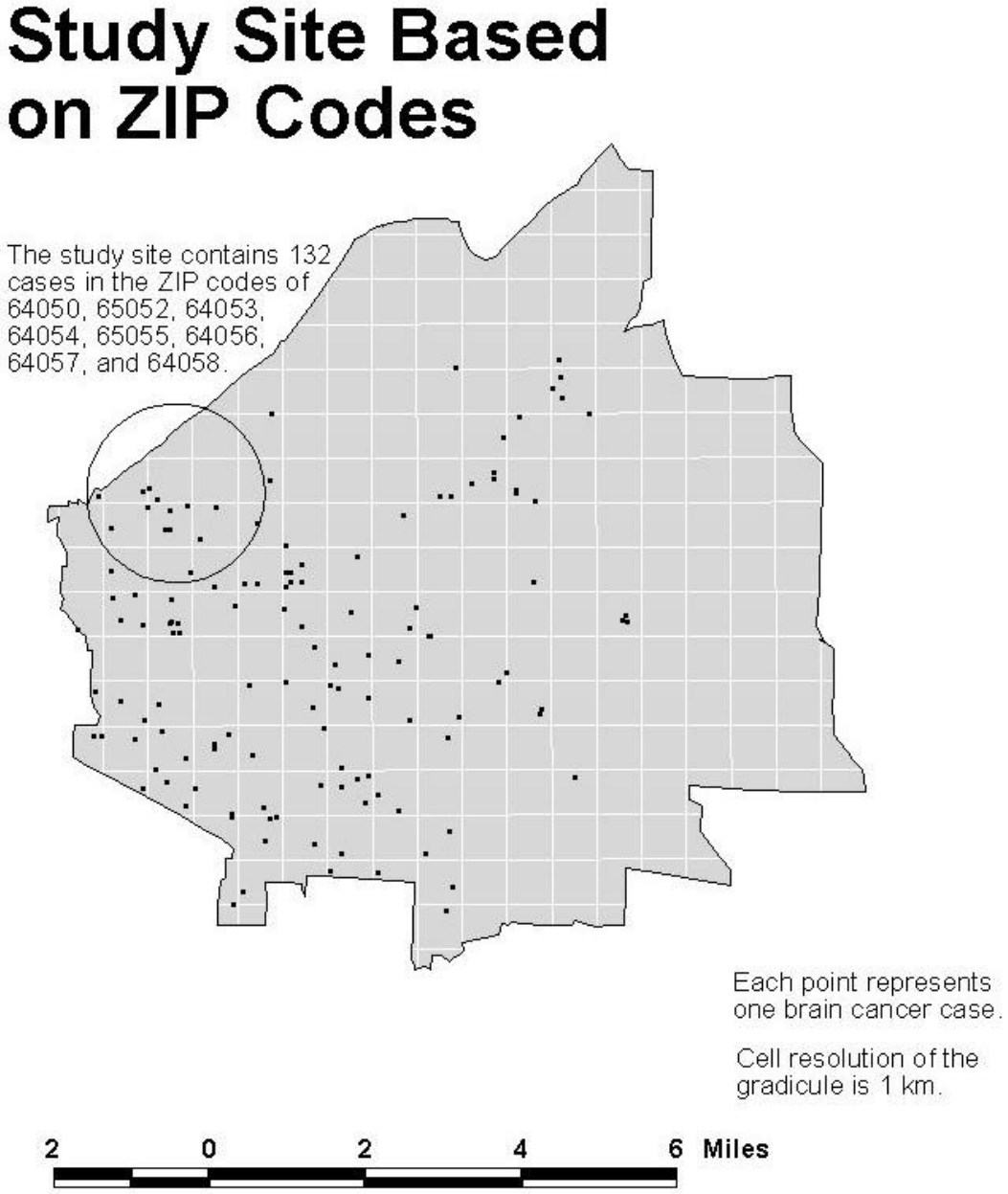


Appendix 1b

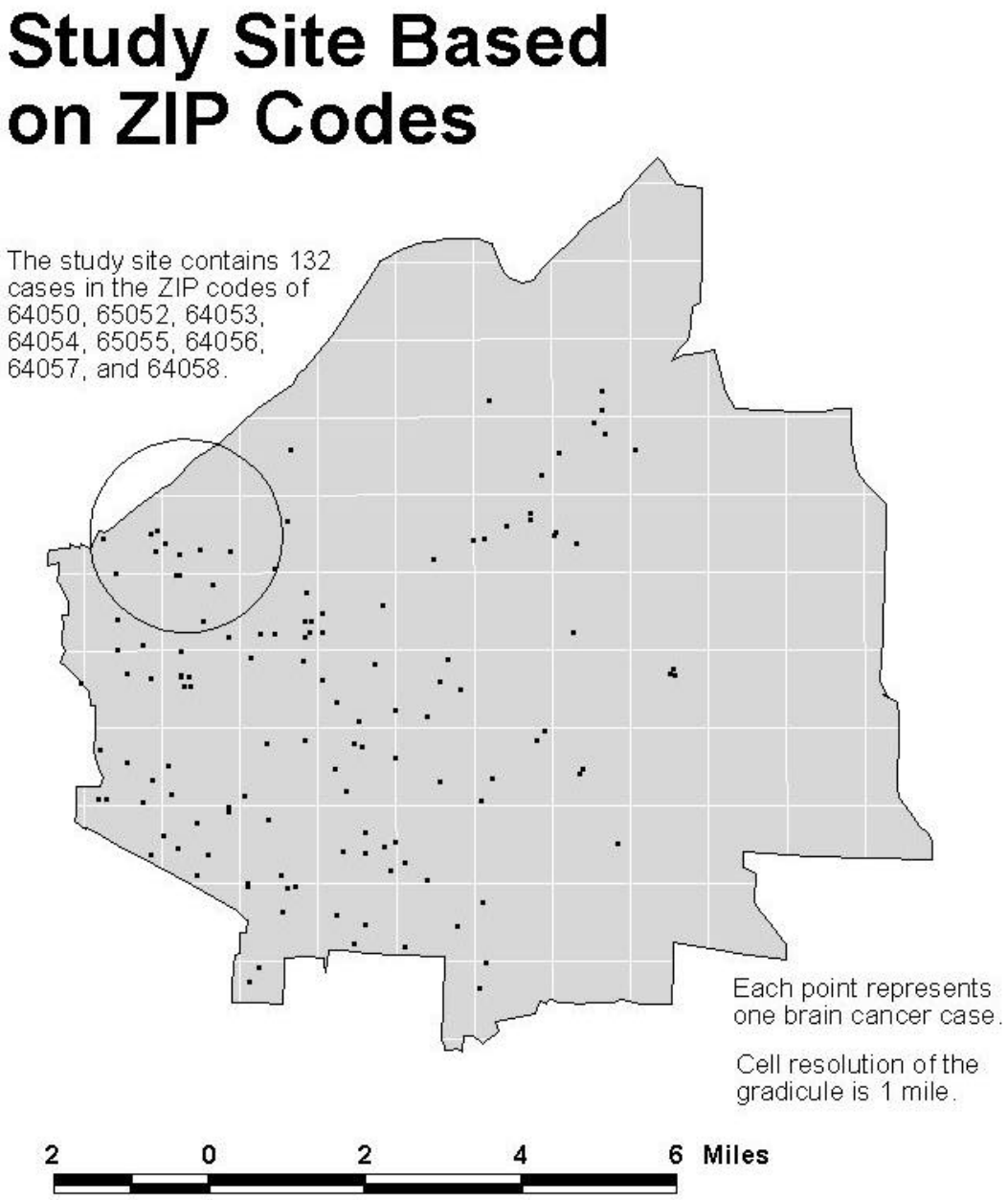
Study Site Based on Political Boundaries



Appendix 2a

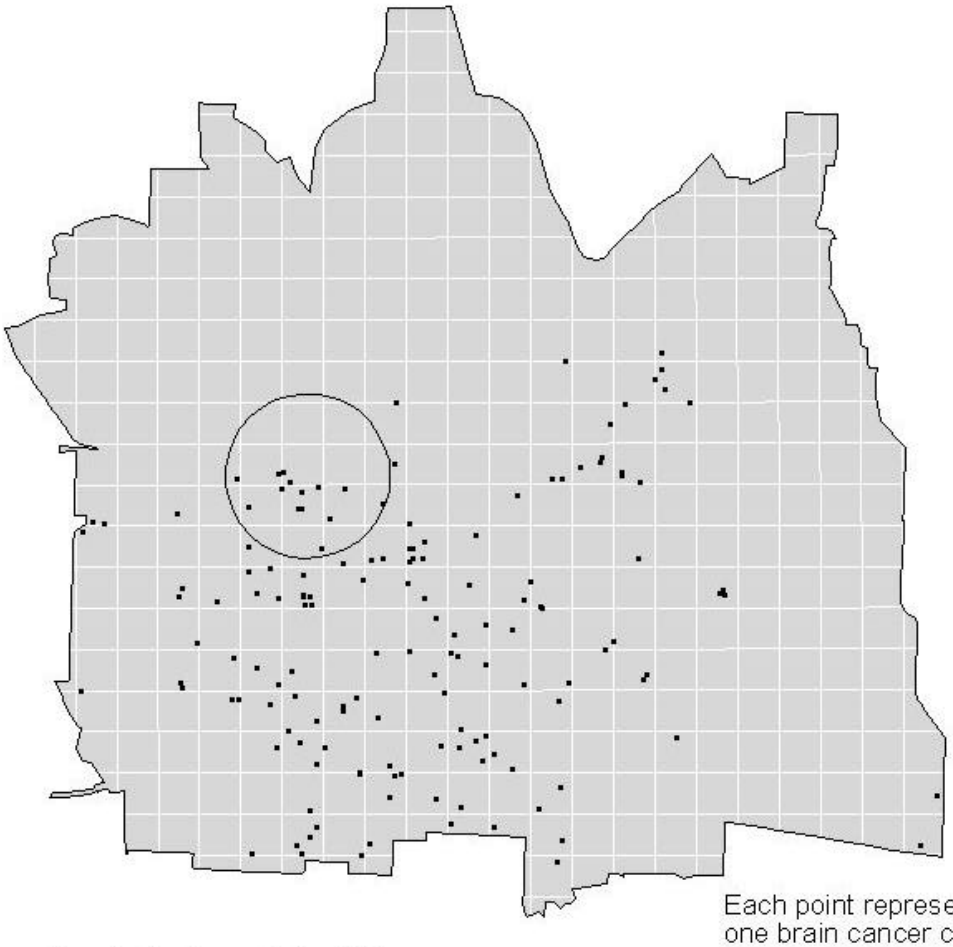

Study Site Based on ZIP Codes
The study site contains 132 cases in the ZIP codes of 64050, 65052, 64053, 64054, 65055, 64056, 64057, and 64058.
Each point represents one brain cancer case.
Cell resolution of the gradicule is 1 km.
2 0 2 4 6 Miles

Appendix 2b


Study Site Based on ZIP Codes
The study site contains 132 cases in the ZIP codes of 64050, 65052, 64053, 64054, 65055, 64056, 64057, and 64058.
Each point represents one brain cancer case.
Cell resolution of the gradicule is 1 mile.
2 0 2 4 6 Miles

Appendix 3a

Study Site Based on Census Block Groups



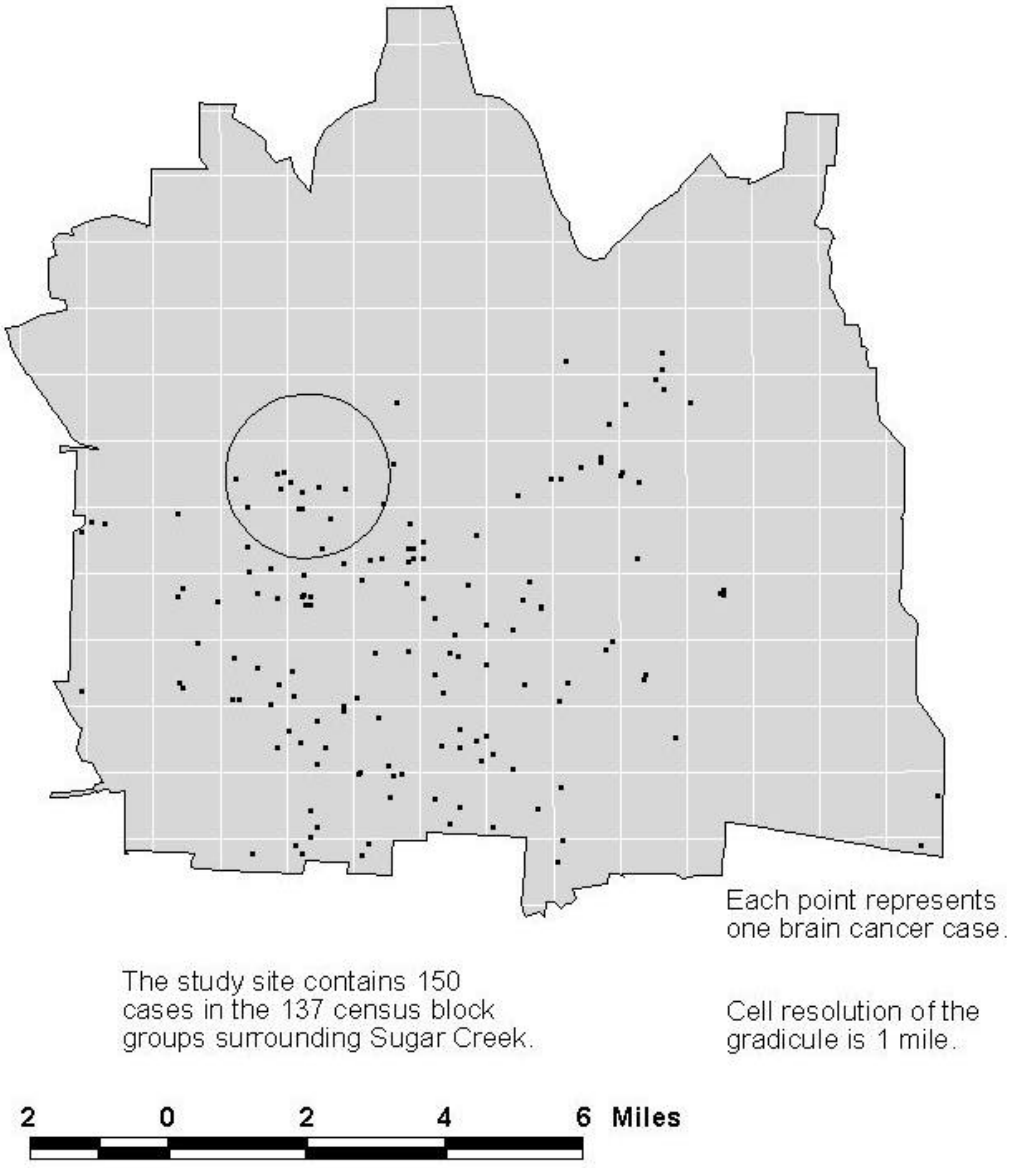
Each point represents one brain cancer case.

The study site contains 150 cases in the 137 census block groups surrounding Sugar Creek.

Cell resolution of the gradicule is 1 km.

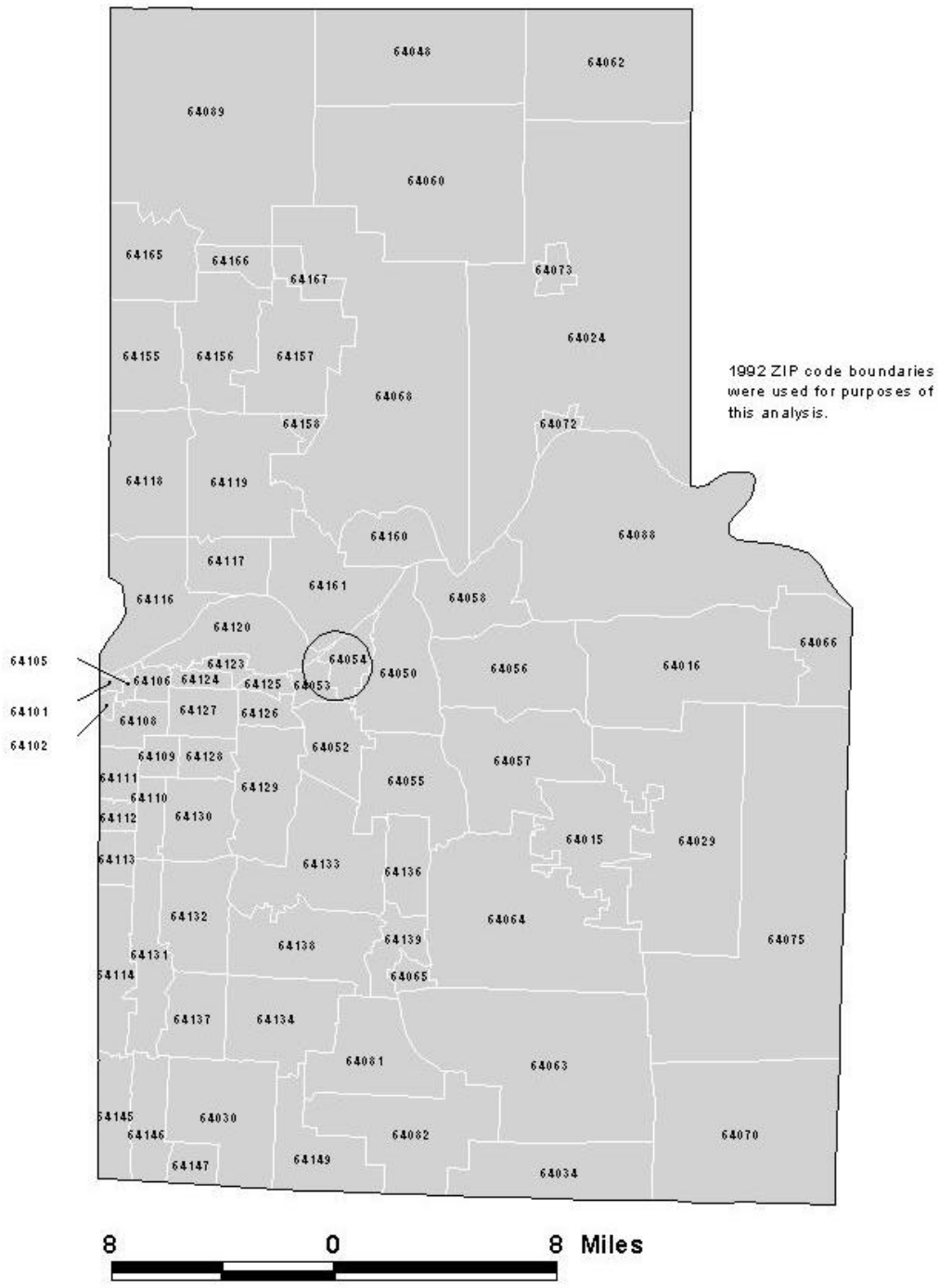
Appendix 3b

Study Site Based on Census Block Groups



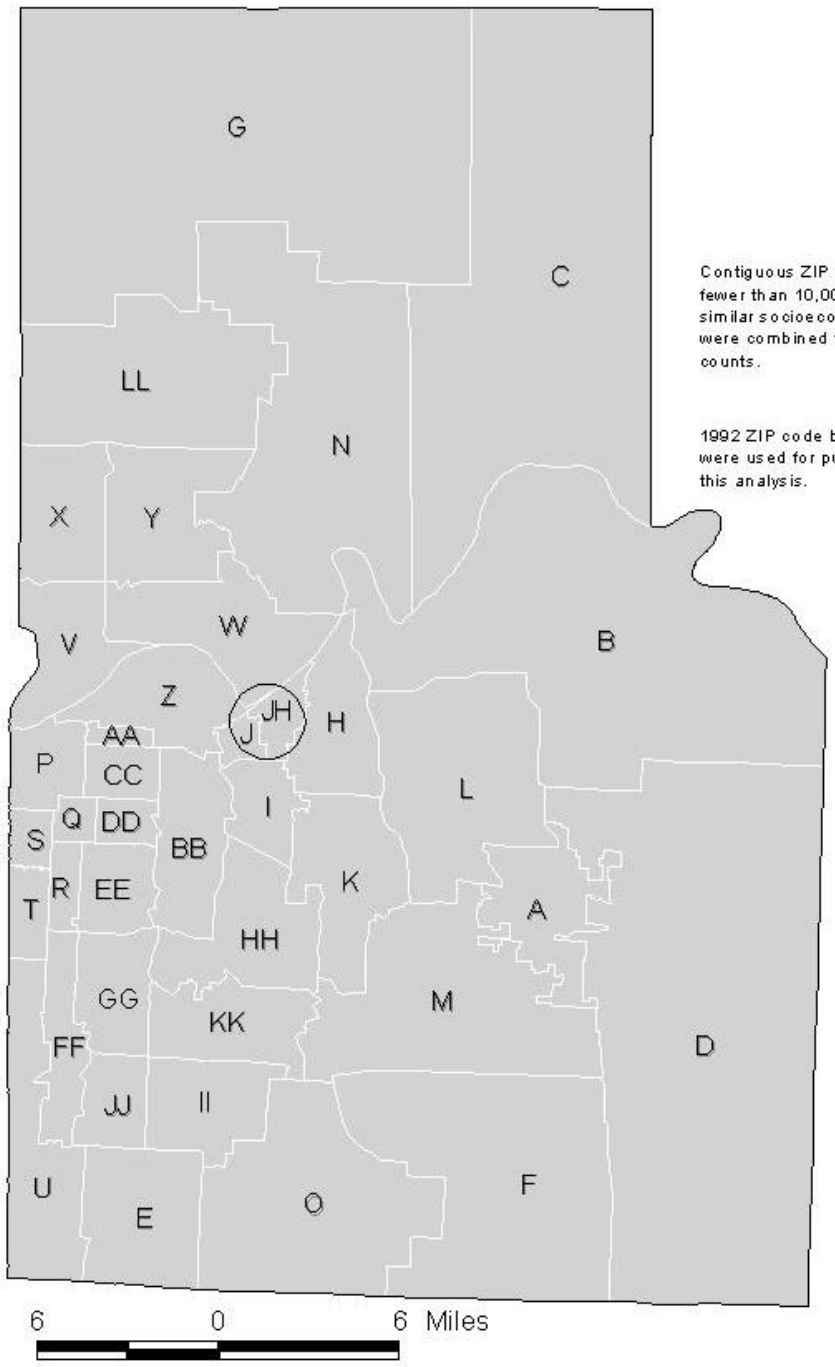
Appendix 4

ZIP Codes



Appendix 5

Aggregated ZIP Codes



Contiguous ZIP codes with fewer than 10,000 people and similar socioeconomic profiles were combined for adjacency counts.

1992 ZIP code boundaries were used for purposes of this analysis.